

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

BA

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07K 5/06, 11/00 C07C 295/26, A61K 37/64 A61K 31/535, C07K 5/02	A1	(11) International Publication Number: WO 93/06127 (43) International Publication Date: 1 April 1993 (01.04.93)
(21) International Application Number: PCT/US92/07463 (22) International Filing Date: 1 September 1992 (01.09.92) (30) Priority data: 761,093 17 September 1991 (17.09.91) US 931,101 25 August 1992 (25.08.92) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann arbor, MI 48105 (US). (72) Inventors: CHENG, Xue-Min ; 2178 Maple Creek Circle, Ann Arbor, MI 48108 (US). REPINE, Joseph, Thomas ; 1201 Creal Crescent, Ann Arbor, MI 48103 (US). TAY- LOR, Michael, Douglas ; 595 Scio Meadow Drive, Ann Arbor, MI 48103 (US). WRIGHT, Jonathan, Leonard ; 2311 Fernwood, Ann Arbor, MI 48103 (US).		(74) Agents: TINNEY, Francis, J.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al. (81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report.</i>
(54) Title: NOVEL AMINO ACID PRODRUG RENIN INHIBITORS (57) Abstract Novel amino acid prodrug renin inhibitors are described, as well as methods for the preparation and pharmaceutical compositions of the same, which are useful as renin inhibitors and thus useful in controlling hypertension, hyperaldosteronism, congestive heart failure, and glaucoma, as well as diagnostic agents.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland	KR	Republic of Korea	SE	Sweden
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovak Republic
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CS	Czechoslovakia	LU	Luxembourg	SU	Soviet Union
CZ	Czech Republic	MC	Monaco	TD	Chad
DE	Germany	MG	Madagascar	TG	Togo
DK	Denmark	ML	Mali	UA	Ukraine
ES	Spain			US	United States of America

NOVEL AMINO ACID PRODRUG RENIN INHIBITORS

BACKGROUND OF THE INVENTION

5

The present invention relates to novel amino acid prodrug renin inhibitors useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment as well as the use of these agents as diagnostic tools. More particularly, the novel compounds of the present invention inhibit the enzyme renin thus controlling hypertension, hyperaldosteronism, congestive heart failure, and glaucoma as well as the use of the compounds as diagnostic tools in mammals.

Renin is a natural enzyme which is released into the blood stream from the kidney. It cleaves its natural substrate, angiotensinogen, releasing a decapeptide, angiotensin I. This in turn is cleaved by converting enzyme in the lung, kidney, and other tissues to an octapeptide, angiotensin II. Angiotensin II raises blood pressure both directly by causing arteriolar constriction and indirectly by stimulating release of the sodium-retaining hormone aldosterone from the adrenal gland causing a rise in extracellular fluid volume. Inhibitors of renin have been sought as agents for control of hypertension and hyperaldosteronism.

Additionally, since HIV protease, like renin, is an aspartyl protease, the novel compounds of the present invention also can be used to treat disorders caused by retroviruses including HTLV I, II, and III.

Renin inhibitors have been shown to be effective agents in the control of hypertension and related

-2-

cardiovascular diseases. However, in general they suffer the drawbacks of poor aqueous solubility and bioavailability. Thus, there is a need to develop a renin inhibitor that has good aqueous solubility and bioavailability.

We have found unexpectedly that certain amino acid derivatives of renin inhibitors have increased water solubility and bioavailability. These derivatives are stable in the gastrointestinal tract but undergo selective, enzyme catalyzed cleavage of the amino acid auxiliary at the gut wall to produce a high local concentration of the parent renin inhibitor and hence improved transport across the gut wall. This effect, combined with the much higher gut lumen concentration of compound due to increased solubility, greatly enhances oral adsorption and hence overall bioavailability. Some of the parent compounds have been disclosed in United States Patent U.S. 5,036,053, European Published Application EP 0399,556, and Repine, J. T., et al, Journal of Medicinal Chemistry, Volume 34, pages 1935-1943 (1991) as renin inhibitors.

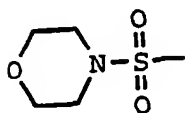
SUMMARY OF THE INVENTION

Accordingly, the present invention is a compound of Formula I

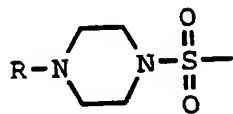
A-E-G-J

I

wherein A is

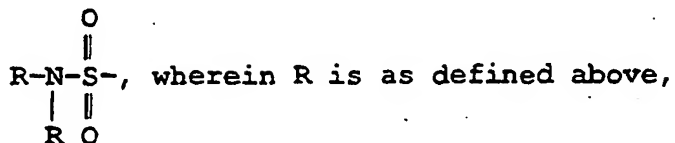


5

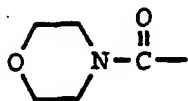


wherein R is hydrogen or alkyl of
from one to six carbon atoms,

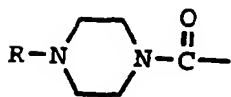
10



15

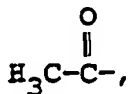


20

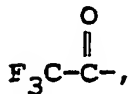


wherein R is as defined above,

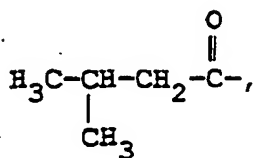
25



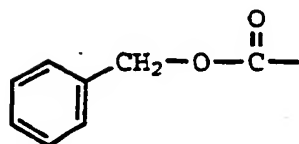
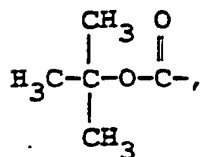
30

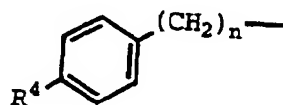
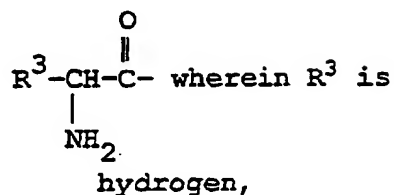
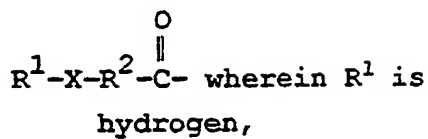
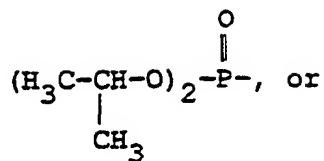


35

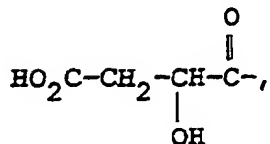
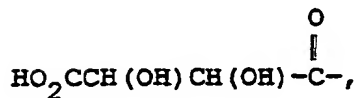
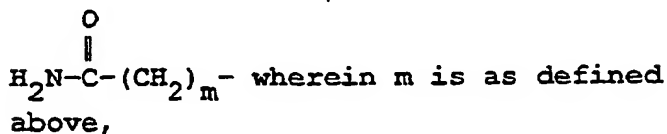
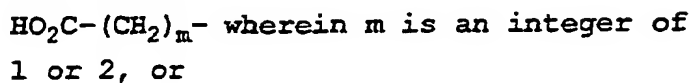
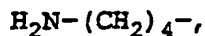


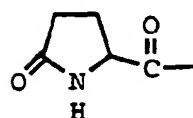
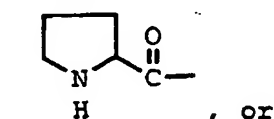
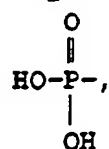
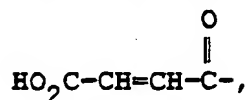
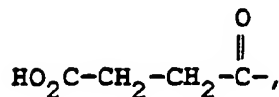
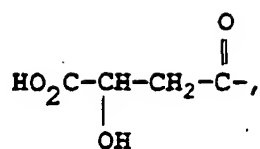
40





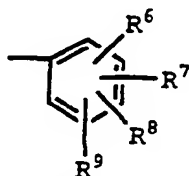
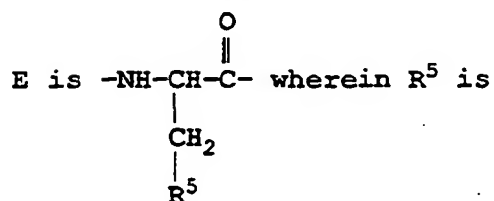
wherein n is zero or an
integer of 1 or 2 and
R⁴ is hydrogen or
hydroxyl,



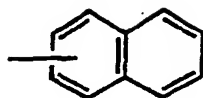


X is O, S, or NH, and

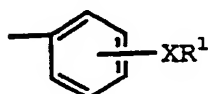
R² is alkyl of from one to six carbon atoms;



wherein R⁶, R⁷, R⁸, or R⁹ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

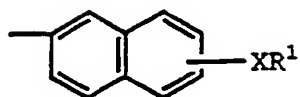


5



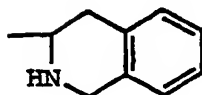
wherein R¹ and X are as defined above,

10

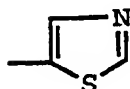


wherein R¹ and X are as defined above,

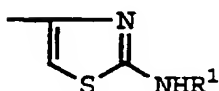
15



20

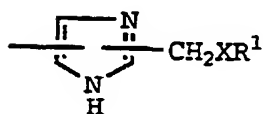


25



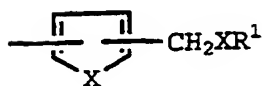
wherein R¹ is as defined above,

30

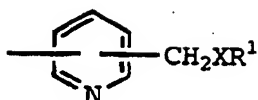


wherein X and R¹ are as defined above,

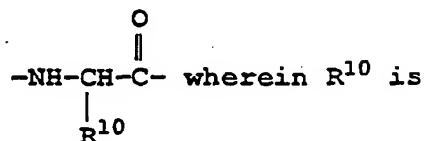
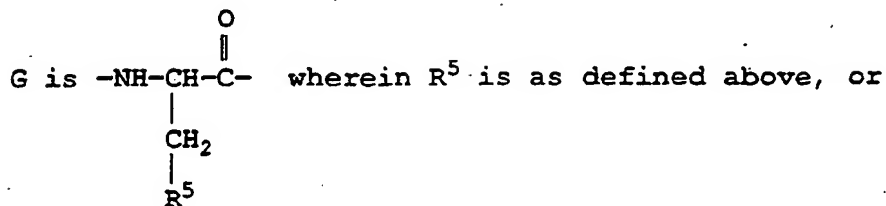
35



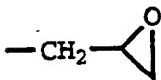
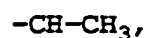
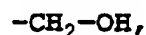
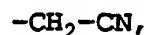
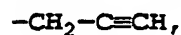
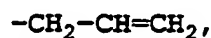
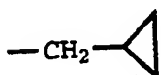
wherein R¹ and X are as defined above, or



wherein R^1 and X are as defined above;



hydrogen,
alkyl of from one to six carbon atoms,
20 $\text{-CO}_2\text{CH}_3$,



35 $\text{-CH}_2\text{-CH}_2\text{X-R}^1$ wherein X and R^1 are as defined above,

$\text{-CH}_2\text{X-R}^1$ wherein X and R^1 are as defined above,

40 -CHX-R^1 wherein X and R^1 are as defined above,

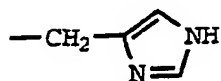
A vertical line leading to CH_3 .



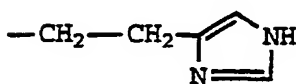
$\text{-CH}_2\text{-CH}_2\text{-S(O)}_n\text{-R}^1$ wherein n and R^1 are as

-8-

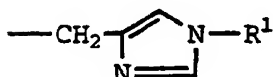
defined above,

 $-(CH_2)_n-CONH_2$ wherein n is as defined above,

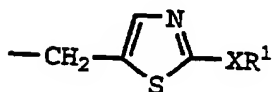
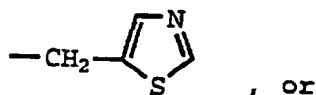
5



10

wherein R^1 is as defined above,

15

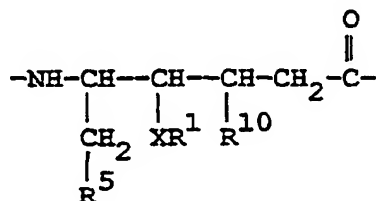


20

wherein X and R^1 are as defined above;

alternatively, E-G is

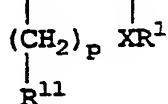
25



30

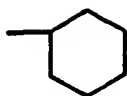
wherein R^1 , X , R^5 , and R^{10} are as defined above;J is $-NH-CH-CH-R^{12}$ wherein R^{11} is

35

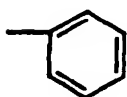
hydrogen,
alkyl,

40

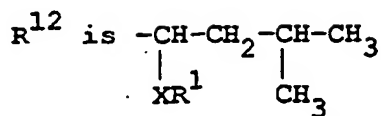
-9-



, or

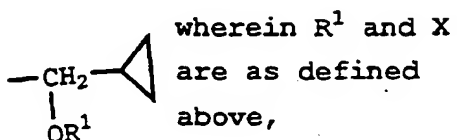


5

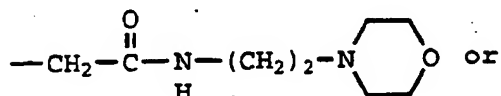


wherein R^1 and X are as defined above,

10

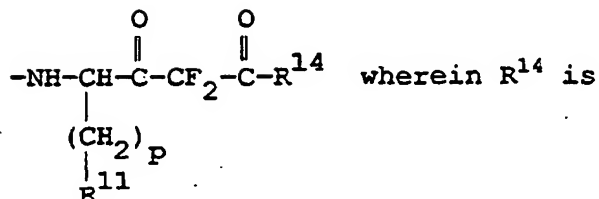


15



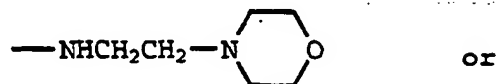
$-CH_2-OC_2H_5$ and R^1 and X are as defined above and p is zero or an integer of one, or

20



25

30



35

and R^{11} and p are as defined above;
provided R^1 with the exclusion of R^1 being hydrogen, is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof.

As amino acid prodrug renin inhibitors the compounds of Formula I are useful for the treatment of hypertension, hyperaldosteronism, congestive heart failure, and diseases caused by retroviruses including HTLC I, II, and III as well as diagnostic tools for the identification of cases of hypertension due to renin excess.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

"Alkoxy" is O-alkyl as defined above for alkyl.

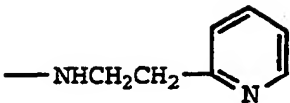
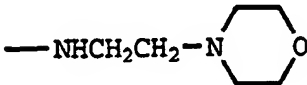
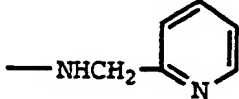
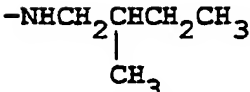
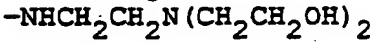
"Halogen" is fluorine, chlorine, bromine, or iodine.

The following table provides a list of abbreviations and definitions thereof used in the present inventions.

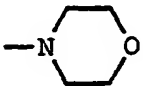
<u>Abbreviation*</u>	<u>Amino Acid</u>
Ala	Alanine
Asp	Aspartic acid

* If the optical activity of the amino acid is other than L(S), the amino acid or abbreviation is preceded by the appropriate configuration D(R) or DL(RS).

-11-

	<u>Abbreviation</u>	<u>Amino Acid</u>
	Glu	Glutamic acid
	Gln	Glutamine
	Gly	Glycine
5	Lys	Lysine
	Phe	Phenylalanine
	Pro	Proline
	Ser	Serine
	Thr	Threonine
10	Tyr	Tyrosine
	 <u>Abbreviation</u> <u>Modified and Unusual Amino Acid</u>	
	Alg	2-Amino-4-pentenoic acid (Allylglycine)
	Atm	2-Amino-3-(2-amino-5-thiazole)propanoic acid
15	Chx	Cyclohexylalanine (Hexahydrophenylalanine)
	Hse	2-Amino-4-hydroxybutyric acid (Homoserine)
	Mal	2-Amino-1,3-propanedioic acid, monomethyl ester
	Pgy	2-Aminopentanoic acid (Propylglycine)
	 <u>Amides With</u>	
20		2-(2-Aminoethyl)pyridine
		N-(2-Aminoethyl)morpholine
25		2-Aminomethylpyridine
		2-Methylbutylamine
		2-Bis(2-hydroxyethyl)-aminoethylamine

-12-

<u>Abbreviation</u>	<u>Esters With</u> <u>Morpholine</u>
	
5	<div>-OCH₃</div> <div>-OC₂H₅</div> <div>-OCH(CH₃)₂</div> <div>-OC(CH₃)₃</div> <div>-OBz</div> <div>Methanol</div> <div>Ethanol</div> <div>2-Propanol</div> <div>tertiary Butanol</div> <div>Benzyl alcohol</div>
10	<div>Cbz</div> <div>Boc</div> <div>TBDMS</div> <div><u>Protecting Group</u></div> <div>Benzyloxycarbonyl</div> <div>tertiary Butyloxycarbonyl</div> <div>tertiary Butyldimethylsilyl</div>
15	<div>CAD</div> <div>SMO</div> <div>Ph</div> <div>Bz</div> <div><u>Miscellaneous</u></div> <div>2(S)-Amino-1-cyclohexyl-6-methyl-3(R),4(S)-heptanediol</div> <div>N-Morpholinesulphonyl</div> <div>Phenyl</div> <div>Benzyl</div>
20	<div><u>Abbreviation</u></div> <div>DMF</div> <div>DMAP</div> <div>DMSO</div> <div>HOBT</div> <div>DCC</div> <div><u>Solvents and Reagents</u></div> <div>N,N-Dimethylformamide</div> <div>4-Dimethylamino pyridine</div> <div>Dimethylsulfoxide</div> <div>Hydroxybenzotriazole</div> <div>N,N'-Dicyclohexylcarbodiimide</div>
25	<div>DCU</div> <div>HOAc</div> <div>Et₃N</div> <div>THF</div> <div>1,3-Dicyclohexylurea</div> <div>Acetic acid</div> <div>Triethylamine</div> <div>Tetrahydrofuran</div>
30	<div>CH₂Cl₂</div> <div>CHCl₃</div> <div>Et₂O</div> <div>CDI</div> <div>TBAF</div> <div>Dichloromethane</div> <div>Chloroform</div> <div>Diethyl ether</div> <div>Carbonyl Diimidazole</div> <div>Tetra-n-butylammonium fluoride</div>
35	<div>KBH₄</div> <div>DMAP</div> <div>EtOAc</div> <div>NaCl</div> <div>Potassium Borohydride</div> <div>N,N-Dimethylaminopyridine</div> <div>Ethyl Acetate</div> <div>Sodium Chloride</div>

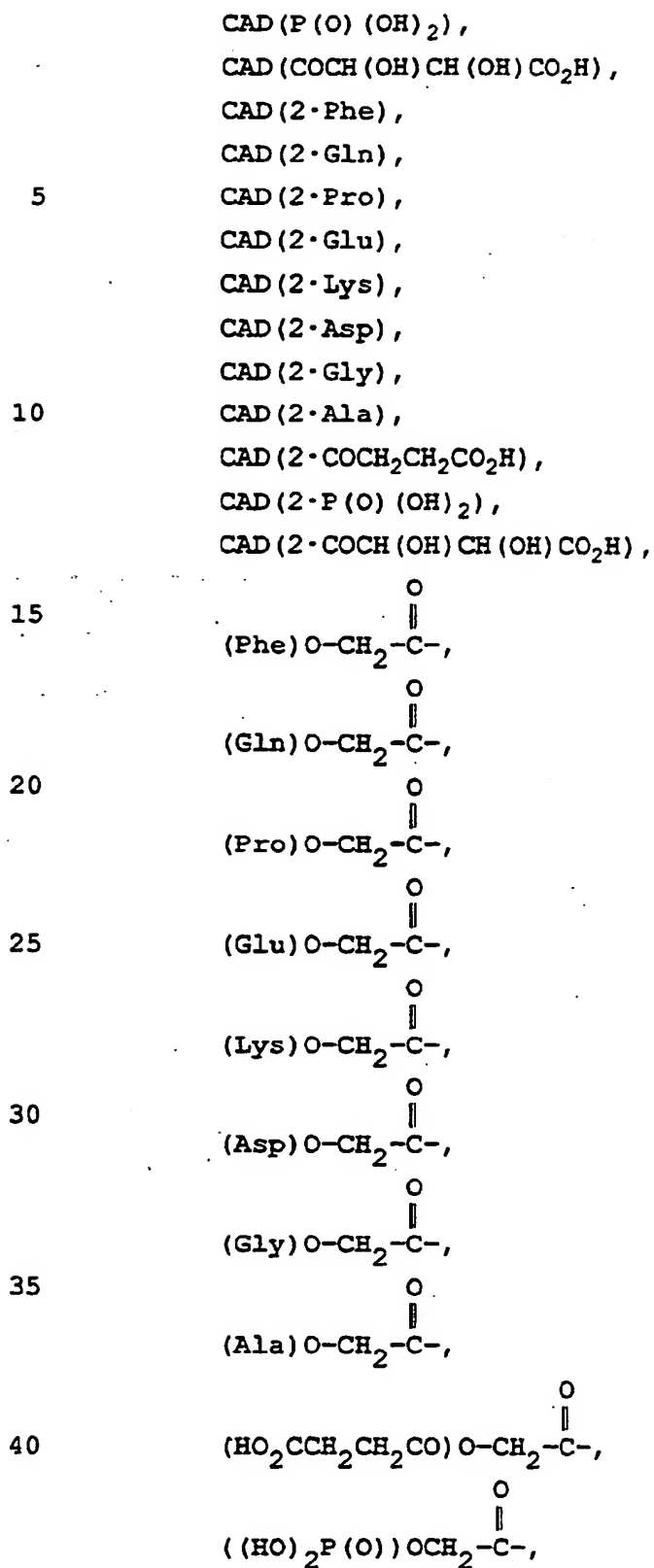
-13-

<u>Abbreviation</u>	<u>Solvents and Reagents</u>
Na_2SO_3	Sodium Sulfite
NaHCO_3	Sodium Bicarbonate
NaIO_4	Sodium periodate
5 Na_2CO_3	Sodium Carbonate
MgSO_4	Magnesium Sulfate
HCl	Hydrochloric acid
EtOH	Ethanol
MeOH	Methanol
10 D_2O	Deuterium Oxide
Na_2SO_4	Sodium Sulfate
TFA	Trifluoroacetic acid
TsOH	Para-toluenesulfonic acid

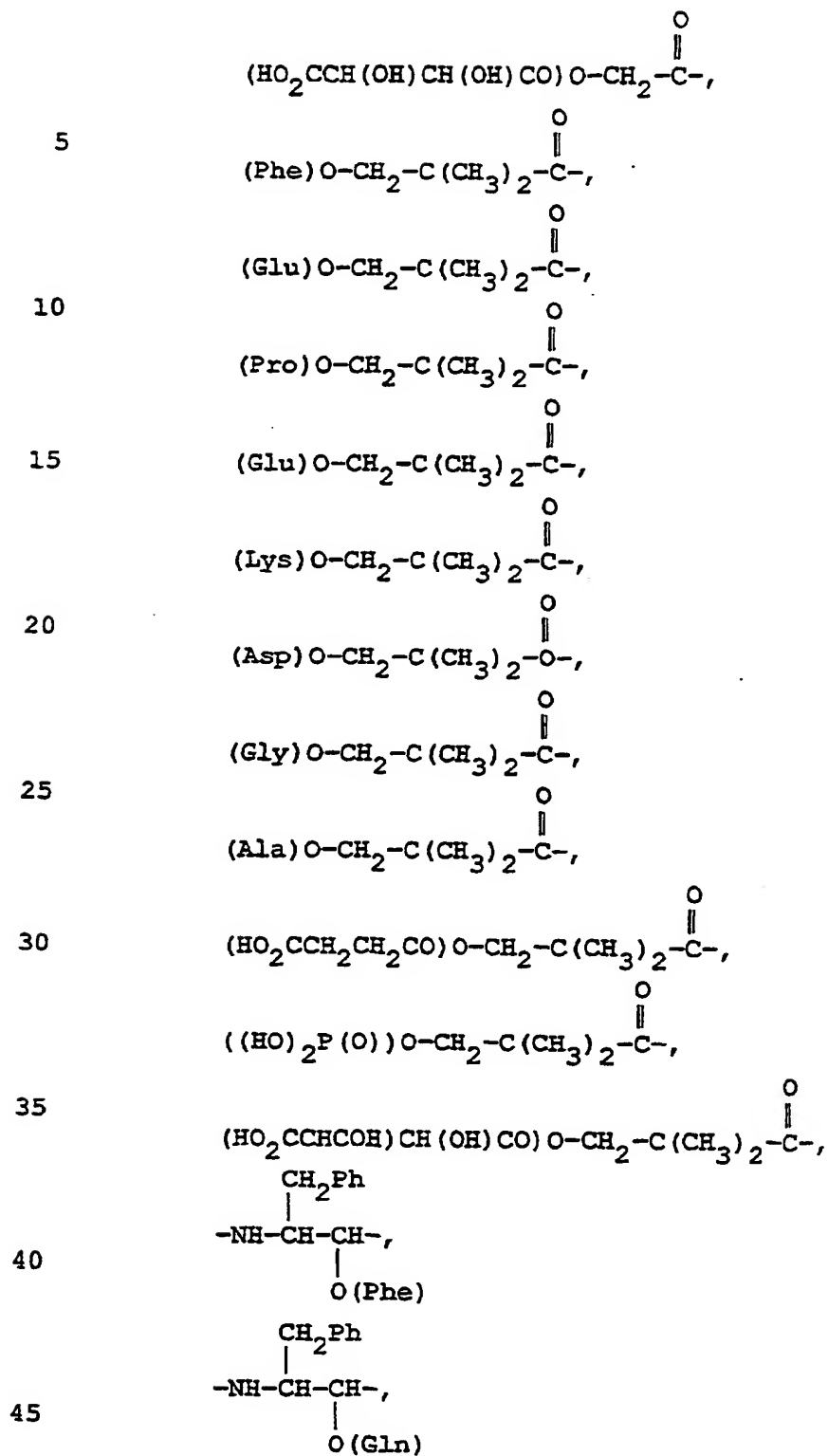
15 An amino acid or organic acid within the bracket
in a structure means the bracketed moiety is attached
via the α carboxylic acid or carboxylic acid,
respectively, to the free hydroxyl or phenolic group
of the preceding amino acid or organic alcohol (where
20 there is more than one free hydroxyl or phenolic
group in the preceding moiety the amino acid or
organic acid may be attached to either or both) to
form an ester such as, for example:

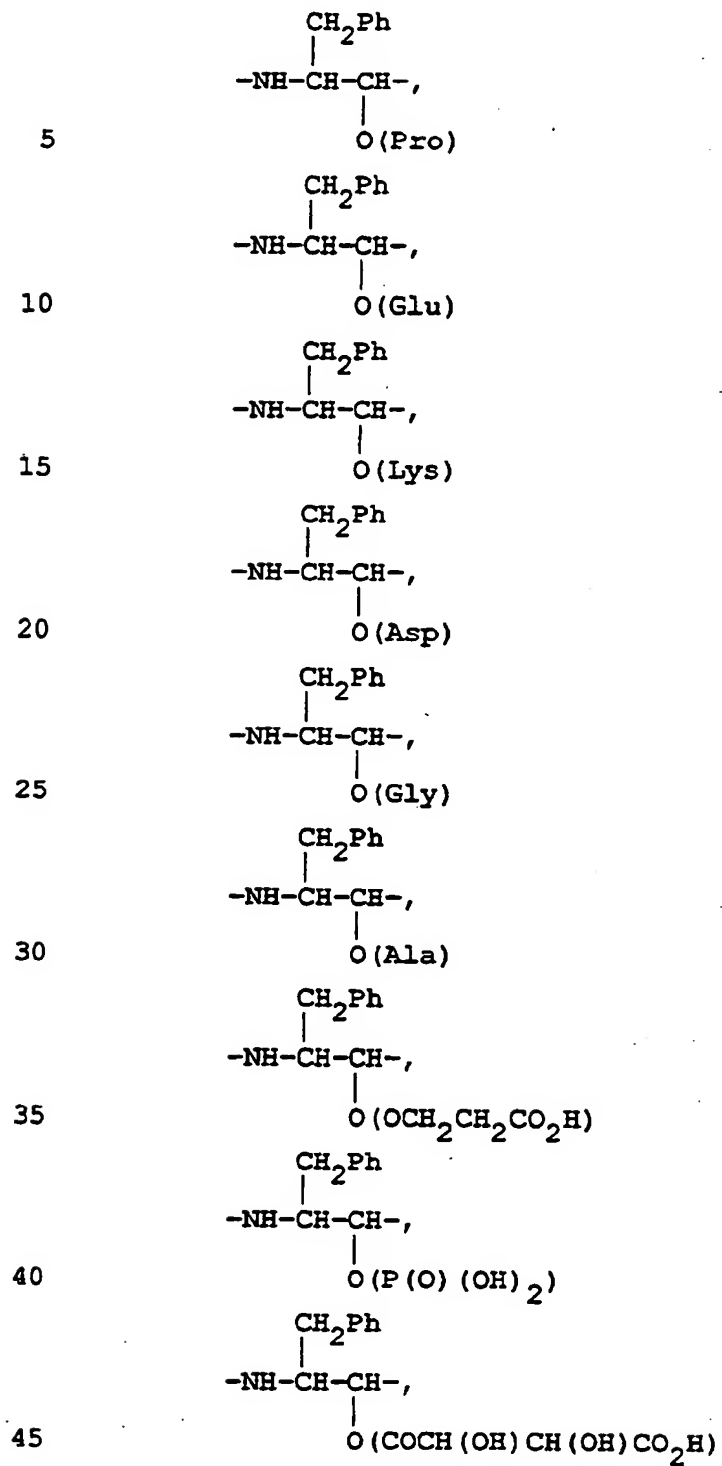
25 Ser(Phe),
 Ser(Gln),
 Ser(Pro),
 Ser(Glu),
 Ser(Lys),
 Ser(Asp),
30 Ser(Gly),
 Ser(Ala),
 Ser($\text{COCH}_2\text{CH}_2\text{CO}_2\text{H}$),
 Ser(P(O)(OH)_2),
 Ser($\text{COCH(OH)CH(OH)CO}_2\text{H}$),
35 Thr(Phe),
 Thr(Gln),
 Thr(Pro),
 Thr(Glu),
 Thr(Lys),

Thr (Asp) ,
Thr (Gly) ,
Thr (Ala) ,
Thr (COCH₂CH₂CO₂H) ,
5 Thr (P (O) (OH) ₂) ,
Thr (COCH (OH) CH (OH) CO₂H) ,
Tyr (Phe) ,
Tyr (Gln) ,
Tyr (Pro) ,
10 Tyr (Glu) ,
Tyr (Lys) ,
Tyr (Asp) ,
Tyr (Gly) ,
Tyr (Ala) ,
15 Tyr (COCH₂CH₂CO₂H) ,
Tyr (P (O) (OH) ₂) ,
Tyr (COCH (OH) CH (OH) CO₂H) ,
Hse (Phe) ,
Hse (Gln) ,
20 Hse (Pro) ,
Hse (Glu) ,
Hse (Lys) ,
Hse (Asp) ,
Hse (Gly) ,
25 Hse (Ala) ,
Hse (COCH₂CH₂CO₂H) ,
Hse (P (O) (OH) ₂) ,
Hse (COCH (OH) CH (OH) CO₂H) ,
CAD (Phe) ,
30 CAD (Gln) ,
CAD (Pro) ,
CAD (Glu) ,
CAD (Lys) ,
CAD (Asp) ,
35 CAD (Gly) ,
CAD (Ala) ,
CAD (COCH₂CH₂CO₂H) ,



-16-





However, when the preceding unbracketed moiety is an organic amine, the bracketed amino acid or organic acid forms an amide bond with the amine such as, for example:

5 Atm(Phe),
 Atm(Gln),
 Atm(Pro),
 Atm(Glu),
 Atm(Lys),
10 Atm(Asp),
 Atm(Gly),
 Atm(Ala),
 Atm(COCH₂CH₂CO₂H),
 Atm(P(O)(OH)₂),
15 Atm(COCH(OH)CH(OH)CO₂H),

For purposes of the present invention a "prodrug" refers to a compound of Formula I which is biotransformed into the active renin inhibitor in a mammal.

20 The compounds of Formula I are capable of further forming pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

25 Pharmaceutically acceptable acid addition salts of the compound of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous and the like, as well as the salts
30 derived from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include
35 sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate,

chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Bergs S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free bases for purposes of the present invention.

Pharmaceutically acceptable base addition salts of acidic compounds are formed with metals or amines such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S. M., et al, Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

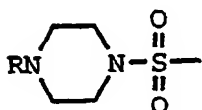
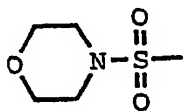
The base addition salts of said acidic compounds are prepared by contacting the free acid form with a

sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acids for purposes of the present invention.

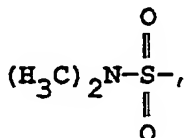
Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

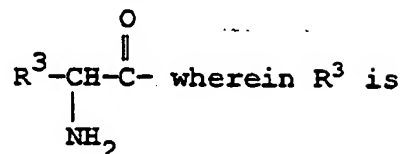
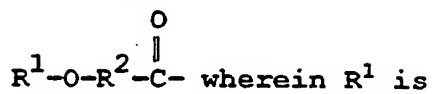
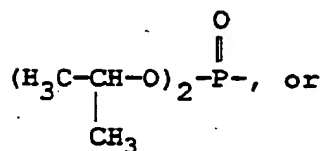
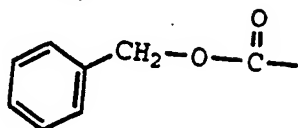
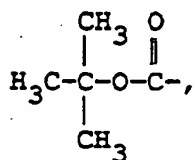
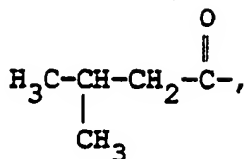
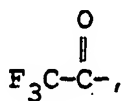
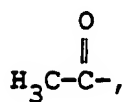
The compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric forms as well as the appropriate mixtures thereof.

A preferred compound of Formula I is one wherein A is

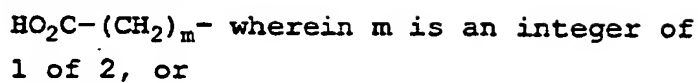
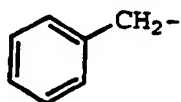


wherein R is hydrogen or alkyl of from one to six carbon atoms,



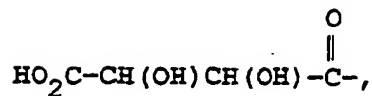


hydrogen,

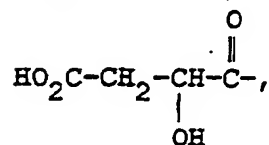


$\text{H}_2\text{N}-\overset{\text{O}}{\parallel}{\text{C}}-(\text{CH}_2)_m-$ wherein m is as defined above,

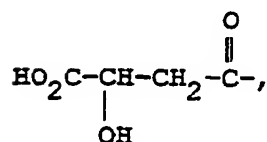
5



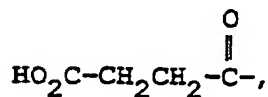
10



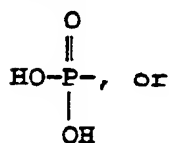
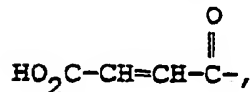
15



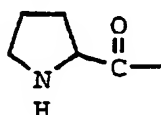
20



25



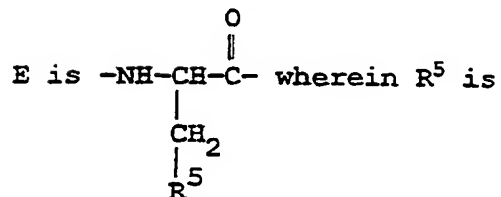
30



and

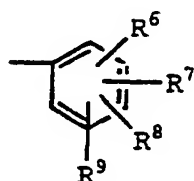
R^2 is alkyl of from one to six carbon atoms;

35



40

45

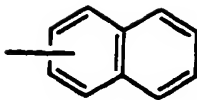


wherein R^6 , R^7 , R^8 , or R^9 are each independently hydrogen,

-23-

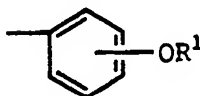
alkyl of from one to six
carbon atoms, alkoxyl of
from one to six carbon
atoms, halogen or
trifluoromethyl,

5



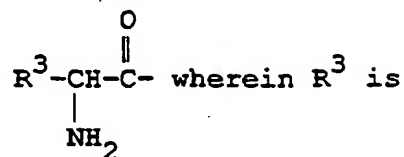
or

10



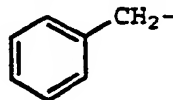
wherein R¹ is
hydrogen,

15



20

hydrogen,



25

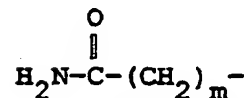
CH₃-,

H₂N-(CH₂)₄-,

HO₂C-(CH₂)ₘ-

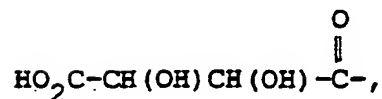
wherein m is
an integer of
1 or 2; or

30



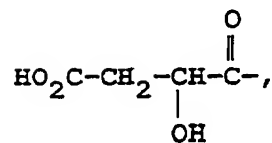
wherein m is
as defined
above,

35

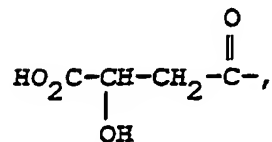


-24-

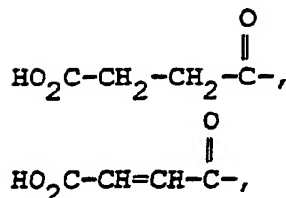
5



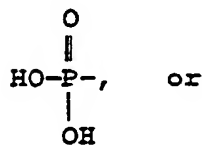
10



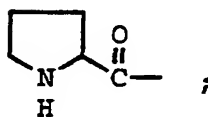
15



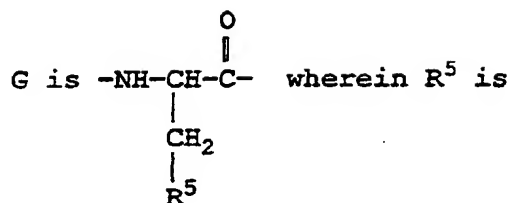
20



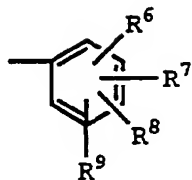
25



30

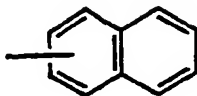


35

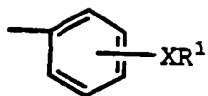


40

wherein R^6 , R^7 , R^8 , or R^9 are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

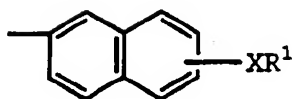


5



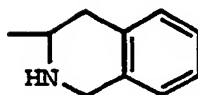
wherein X is O, S, or NH and
R¹ is as defined above

10

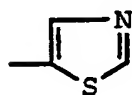


wherein R¹ and X are as
defined above,

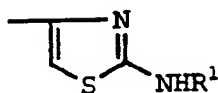
15



20

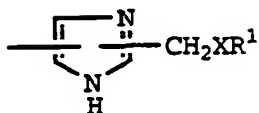


25



wherein R¹ is as defined
above,

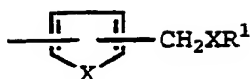
30



35

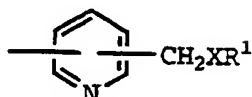
wherein X and R¹ are as
defined above,

-26-



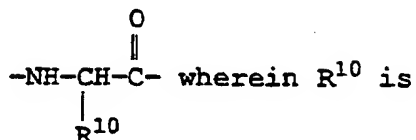
wherein R^1 and X are as defined above,

5



wherein R^1 and X are as defined above, or

10

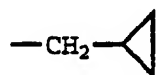


hydrogen,

alkyl of from one to six carbon atoms,

15

$\text{---CO}_2\text{CH}_3$,



20

$\text{---CH}_2\text{---CH=CH}_2$,

$\text{---CH}_2\text{---C}\equiv\text{CH}$,

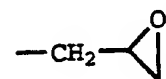
$\text{---CH}_2\text{---CN}$,

$\text{---CH}_2\text{---OH}$,

---CH---CH_3 ,

25

$\begin{array}{c} | \\ \text{OH} \end{array}$



30

$\text{---CH}_2\text{---CH}_2\text{X---R}^1$ wherein X and R^1 are as defined above,

$\text{---CH}_2\text{X---R}^1$ wherein X and R^1 are as defined above,

35

---CH---X---R^1 wherein X and R^1 are as defined above,

$\begin{array}{c} | \\ \text{CH}_3 \end{array}$

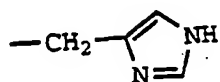
$\text{---CH}_2\text{---CH}_2\text{CH}_2\text{CH}_2\text{---NH}_2$,

40

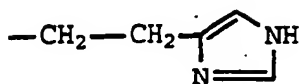
$\text{---CH}_2\text{---CH}_2\text{---S(O)}_n\text{---R}^1$ wherein n is zero or an integer of 1 or 2 and R^1 is as defined above,

-27-

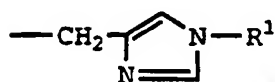
-(CH₂)_n-CONH₂ wherein n is as defined above,



5

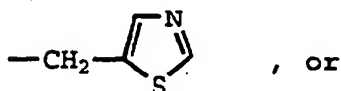


10

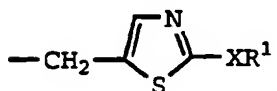


wherein R¹ is as defined above,

15



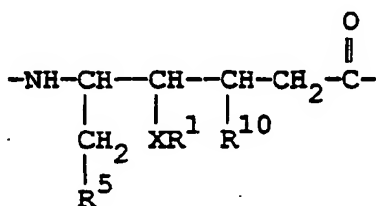
20



wherein X and R¹ are as defined above;

alternatively, E-G is

25

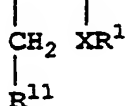


30

wherein R¹, X, R⁵, and R¹⁰ are as defined above;

J is -NH-CH-CH-R¹² wherein R¹¹ is

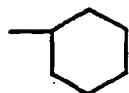
35



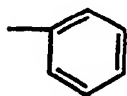
hydrogen,
alkyl,

40

-28-



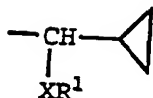
, or



5

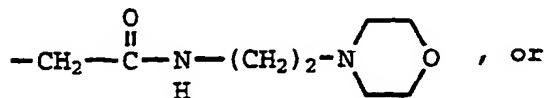
R^{12} is $\begin{array}{c} -CH-CH_2-CH-CH_3 \\ | \quad \quad | \\ OR^1 \quad CH_3 \end{array}$ wherein R^1 is as defined above,

10



wherein R^1 is as defined above,

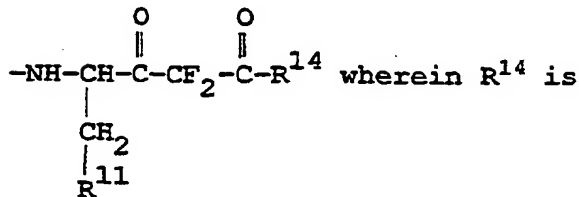
15



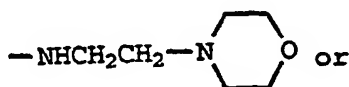
, or

$-CH_2-OC_2H_5$ and R^1 and X are as defined above
or

20

wherein R^{14} is

25



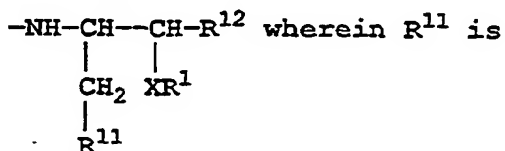
or

30

$-OC_2H_5$ and R^{11} is as defined above; provided
 R^1 with the exclusion of R^1 being hydrogen
is encompassed within the definition of at
least one of A, E, G, or J.

35

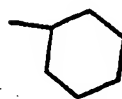
A more preferred compound of Formula I is one
wherein J is



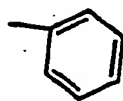
40

alkyl,

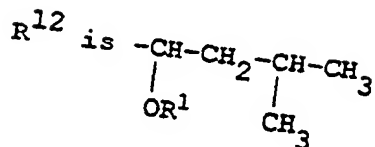
5



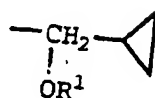
, or



10

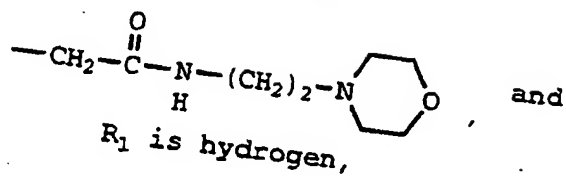


15

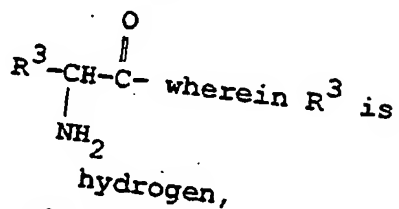


or

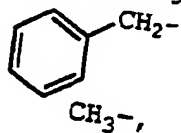
20



25

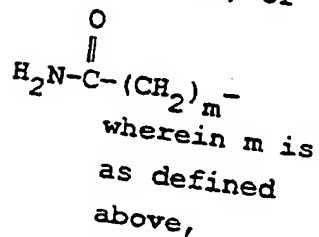


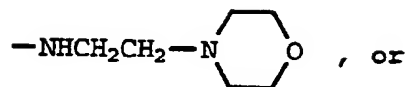
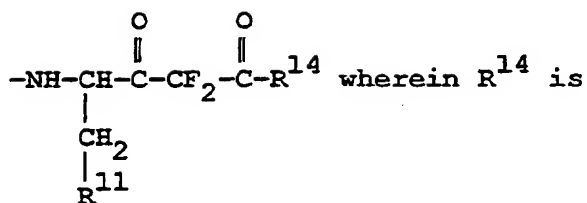
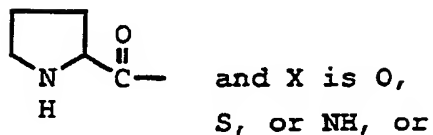
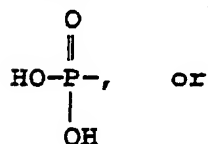
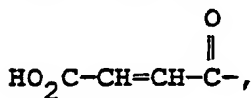
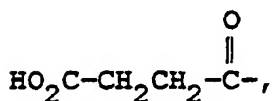
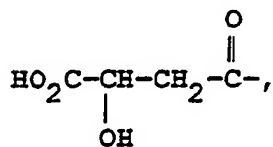
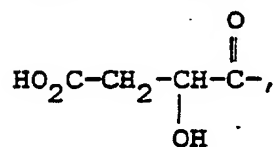
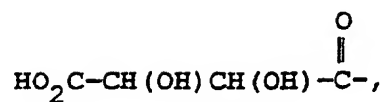
30

 $\text{CH}_3\text{---}$, $\text{H}_2\text{N---(CH}_2)_4\text{---}$, $\text{HO}_2\text{C---(CH}_2)_m\text{---}$

wherein m is
an integer of
1 or 2, or

35





$-\text{OC}_2\text{H}_5$ and

R^{11} is as defined above.

Particularly valuable are:

SMO-Phe-Ser(Phe)-CAD;

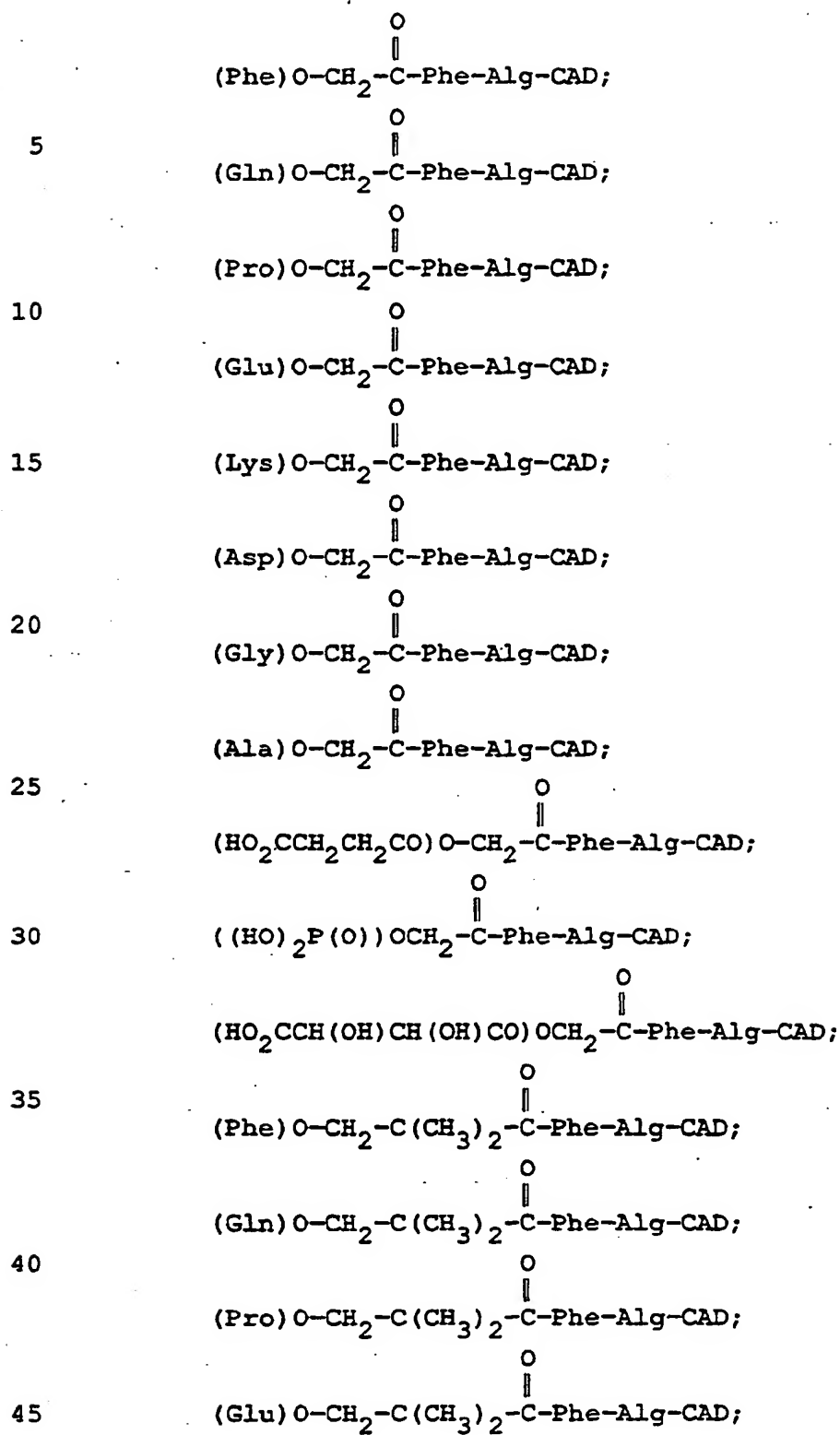
SMO-Phe-Ser(Gln)-CAD;

SMO-Phe-Ser(Pro)-CAD;

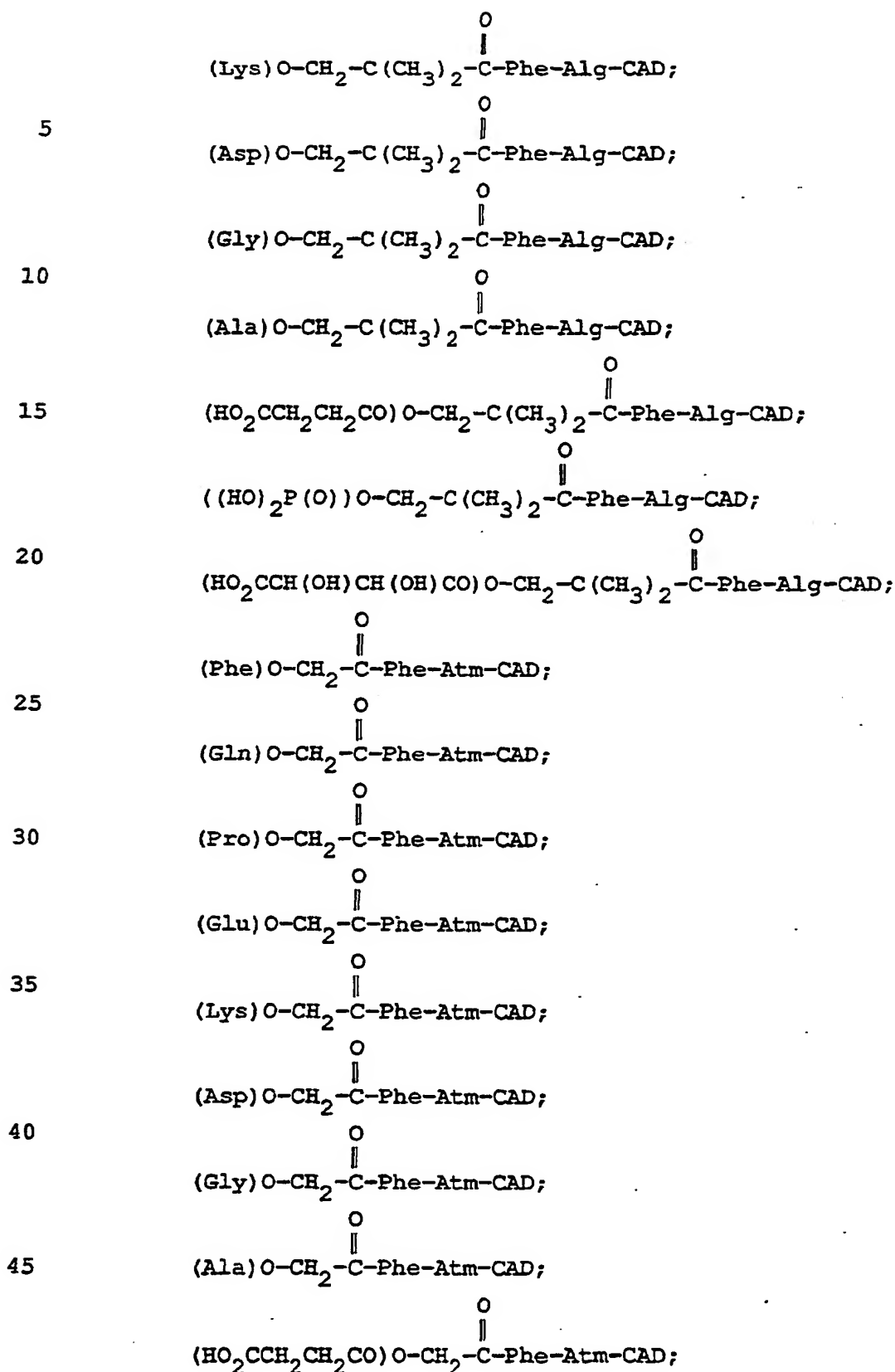
-31-

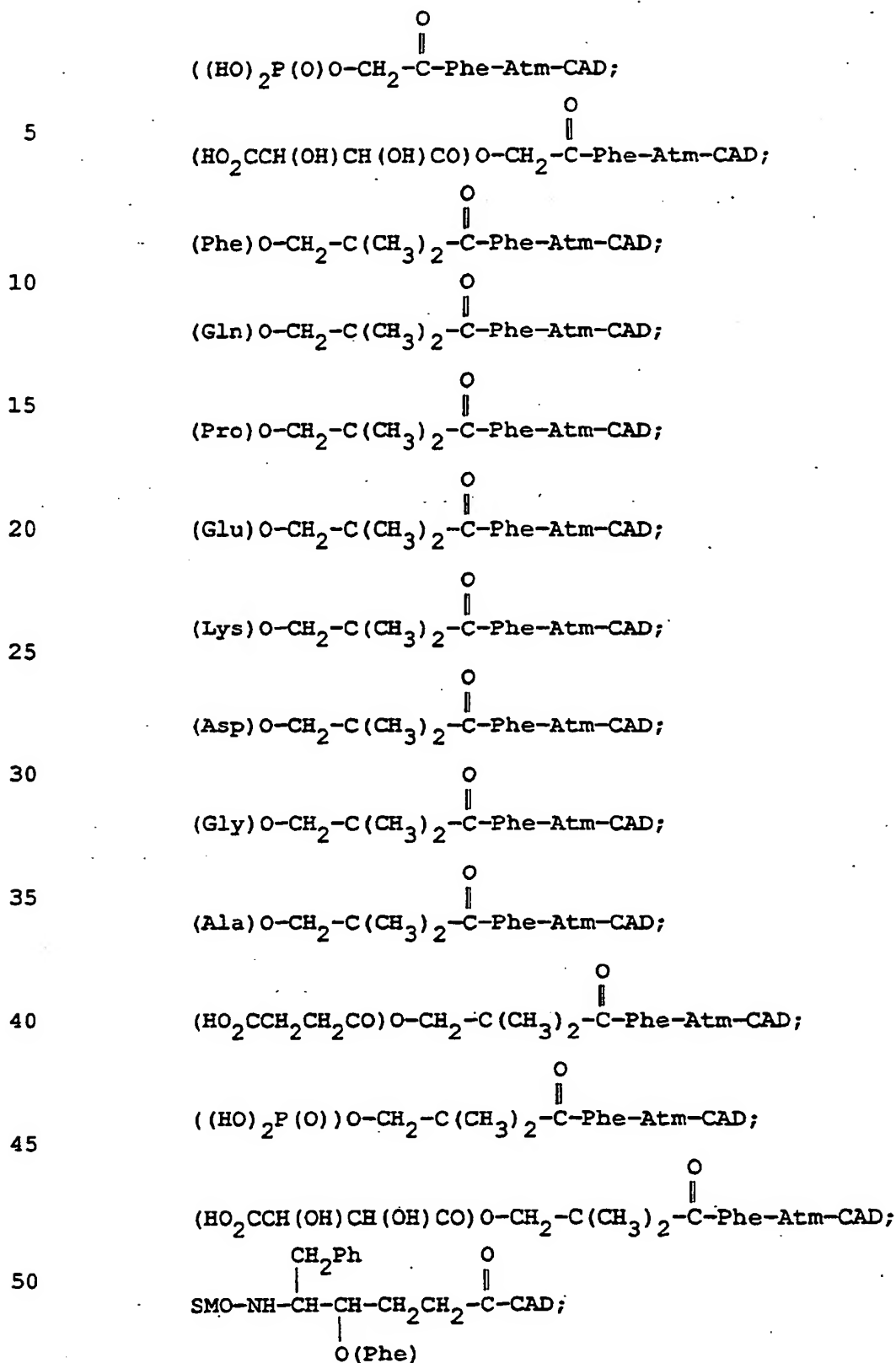
SMO-Phe-Ser (Glu) -CAD;
SMO-Phe-Ser (Lys) -CAD;
SMO-Phe-Ser (Asp) -CAD;
SMO-Phe-Ser (Gly) -CAD;
5 SMO-Phe-Ser (Ala) -CAD;
SMO-Phe-Ser (COCH₂CH₂CO₂H) -CAD;
SMO-Phe-Ser (P (O) (OH)₂) -CAD;
SMO-Phe-Ser (COCH (OH) CH (OH) CO₂H) -CAD;
SMO-Phe-Thr (Phe) -CAD;
10 SMO-Phe-Thr (Gln) -CAD;
SMO-Phe-Thr (Pro) -CAD;
SMO-Phe-Thr (Glu) -CAD;
SMO-Phe-Thr (Lys) -CAD;
SMO-Phe-Thr (Asp) -CAD;
15 SMO-Phe-Thr (Gly) -CAD;
SMO-Phe-Thr (Ala) -CAD;
SMO-Phe-Thr (COCH₂CH₂CO₂H) -CAD;
SMO-Phe-Thr (P (O) (OH)₂) -CAD;
SMO-Phe-Thr (COCH (OH) CH (OH) CO₂H) -CAD;
20 Boc-Tyr (Phe) -Pgy-CAD;
Boc-Tyr (Gln) -Pgy-CAD;
Boc-Tyr (Pro) -Pgy-CAD;
Boc-Tyr (Glu) -Pgy-CAD;
Boc-Tyr (Lys) -Pgy-CAD;
25 Boc-Tyr (Asp) -Pgy-CAD;
Boc-Tyr (Gly) -Pgy-CAD;
Boc-Tyr (Ala) -Pgy-CAD;
Boc-Tyr (COCH₂CH₂CO₂H) -Pgy-CAD;
Boc-Tyr (P (O) (OH) CH (OH) CO₂H) -Pgy-CAD;
30 Boc-Tyr (COCH (OH) CH (OH) CO₂H) -Pgy-CAD;
SMO-Phe-Hse (Phe) -CAD;
SMO-Phe-Hse (Gln) -CAD;
SMO-Phe-Hse (Pro) -CAD;
SMO-Phe-Hse (Glu) -CAD;
35 SMO-Phe-Hse (Lys) -CAD;
SMO-Phe-Hse (Asp) -CAD;
SMO-Phe-Hse (Gly) -CAD;

- SMO-Phe-Hse (Ala) -CAD;
SMO-Phe-Hse (COCH₂CH₂CO₂H) -CAD;
SMO-Phe-Hse (P (O) (OH)₂) -CAD;
SMO-Phe-Hse (COCH (OH) CH (OH) CO₂H) -CAD;
5 SMO-Phe-Mal-CAD (2·Phe);
SMO-Phe-Mal-CAD (2·Gln);
SMO-Phe-Mal-CAD (2·Pro);
SMO-Phe-Mal-CAD (2·Glu);
SMO-Phe-Mal-CAD (2·Lys);
10 SMO-Phe-Mal-CAD (2·Asp);
SMO-Phe-Mal-CAD (2·Gly);
SMO-Phe-Mal-CAD (2·Ala);
SMO-Phe-Mal-CAD (2·COCH (OH) CH (OH) CO₂H);
SMO-Phe-Mal-CAD (2·P (O) (OH)₂);
15 SMO-Phe-Mal-CAD (2·COCH (OH) CH (OH) CO₂H);
SMO-Phe-Atm-CAD (2·Phe);
SMO-Phe-Atm-CAD (2·Gln);
SMO-Phe-Atm-CAD (2·Pro);
SMO-Phe-Atm-CAD (2·Glu);
20 SMO-Phe-Atm-CAD (2·Lys);
SMO-Phe-Atm-CAD (2·Asp);
SMO-Phe-Atm-CAD (2·Gly);
SMO-Phe-Atm-CAD (2·Ala);
SMO-Phe-Atm-CAD (2·COCH₂CH₂CO₂H);
25 SMO-Phe-Atm-CAD (2·P (O) (OH)₂);
SMO-Phe-Atm-CAD (2·COCH (OH) CH (OH) CO₂H);
SMO-Phe-Atm(Phe) -CAD;
SMO-Phe-Atm(Gln) -CAD;
SMO-Phe-Atm(Pro) -CAD;
30 SMO-Phe-Atm(Glu) -CAD;
SMO-Phe-Atm(Lys) -CAD;
SMO-Phe-Atm(Asp) -CAD;
SMO-Phe-Atm(Gly) -CAD;
SMO-Phe-Atm(Ala) -CAD;
35 SMO-Phe-Atm(COCH₂CH₂CO₂H) -CAD;
SMO-Phe-Atm(P (O) (OH)₂) -CAD;
SMO-Phe-Atm(COCH (OH) CH (OH) CO₂H) -CAD;

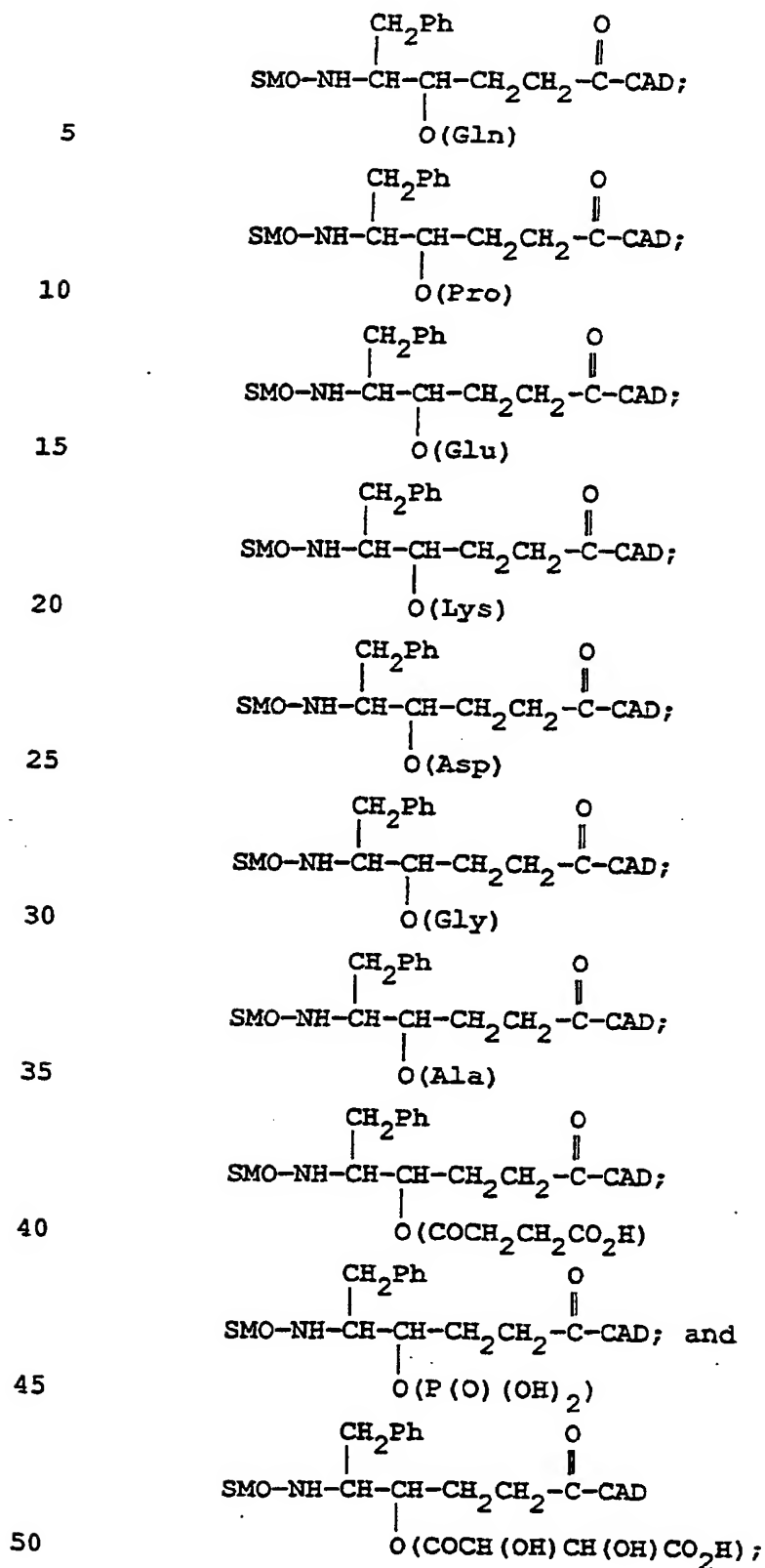


-34-





-36-



or a pharmaceutically acceptable salt thereof.

Amidon, G.L., et al, Journal of Pharmaceutical Sciences, Vol. 69, pages 1363-1368 (1980) described a procedure for improving the intestinal absorption of water - insoluble drugs. This strategy converts the insoluble compound to a soluble derivative which subsequently is converted enzymatically to the parent compound in vivo. Thus, the soluble derivatives of the water insoluble drug acts as a prodrug which is converted by enzymes in the surface coat of the brush border region of the microvillous membrane in the intestine to the desired drug. The ability of a compound of Formula I which is a water soluble amino acid derivative of a renin inhibitor to act as a prodrug that is converted by intestinal enzymes to the parent renin inhibitor is tested using the following procedure.

Stability in Intestinal Perfusate - Perfusate is generated by oscillating 15 to 20 mL MES buffer through rat jejunum in situ at 30 mL/min using a withdrawal/infusion pump (Harvard Apparatus, Model 4200-015). At 1.5 h, the perfusate is collected and spiked with prodrug at 37 µg/mL. The solution is incubated at 37°C and disappearance of prodrug over time is monitored by direct injection (25 µL) onto HPLC.

Stability in Suspensions of Brush Border Membranes (BBM) - BBM are prepared from rat or rabbit small intestine by the method of Kessler, et al, Biochim. Biophys. Acta 506:136-154, (1978) with some modifications. Vesicles (50 µL) are combined with 450 µL drug or prodrug (10 µg/mL) and incubated at 37°C. At selected time points, 100 µL prodrug/BBM suspension is removed and diluted with 100 µL acetonitrile, then 150 µL MES, centrifuged, and 50 µL is injected onto HPLC.

HPLC Conditions - Samples are analyzed by high pressure liquid chromatography using a two pump binary-gradient system (HP 1090 Liquid Chromatograph), a Lambda-Max LC Spectrophotometer (Waters, Model 481) set to 214 nm, and a ChromJet integrator (SpectraPhysics). The Econosil column (C8, 4.6 x 250 mm) is at room temperature. Solvent A is water/acetonitrile/triethylamine (TEA) (90:10:0.1) and solvent B is acetonitrile/water/TEA (70:30:0.1). The mobile phase is degassed and maintained with zero grade helium. Isocratic conditions consisted of 65% solvent A and 35% solvent B. At a flow rate of 1.0 mL/min, the retention times are 56 min for the drug and 9.6 min for the prodrug. MES buffer is 10 mM (2-[N-Morpholino]ethanesulfonic acid, made iso-osmotic with 10 mM KCl and 140 mM NaCl and adjusted to pH 6.5 with 1N NaOH.

The data in Table I show some representative water soluble amino acid prodrug renin inhibitors which are converted to the parent renin inhibitor by intestinal enzymes and also by brush border enzymes.

-39-

TABLE I

Example	Compound	Perfusate t½ (minutes)	BBM t½ (minutes)	Selectivity (Perfusate t½/ BBM t½)
1	SMO-Phe-Ser (Lys·2HCl) -CAD	36.4	36.9	0.99
2	SMO-Phe-Ser (Asp·HCl) -CAD	576.0	291.0	2.00
4	SMO-Phe-Ser (Glu·TFA) -CAD	388.0	235.0	1.70
5	SMO-Phe-Ser (Gln·TFA) -CAD	69.7	72.6	0.96
6	SMO-Phe-Ser (Ala·TFA) -CAD	50.2	54.1	0.93
9	$\begin{array}{c} \text{CH}_2\text{Ph} \\ \\ \text{SMO-NH-CH-CH-CH}_2\text{-CH}_2\text{-C-CAD} \\ \quad \quad \quad \parallel \\ \text{*} \quad \quad \quad \text{O} \\ \quad \quad \quad \text{O (Asp)} \end{array}$	100.4 h	15.4 h	6.67
11	$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Asp})\text{O-CH}_2\text{-C-Phe-Alg-CAD}\cdot\text{HCl} \end{array}$	32.4	4.7	7.00
10	$\begin{array}{c} \text{CH}_3 \quad \text{O} \\ \quad \parallel \\ (\text{Asp})\text{O-CH}_2\text{-C-C-Phe-Atm-CAD}\cdot\text{HCl} \\ \\ \text{CH}_3 \end{array}$	508.5	14.0	36.32
13	$\begin{array}{c} \text{CH}_3 \quad \text{O} \\ \quad \parallel \\ (\text{Asp})\text{O-CH}_2\text{-C-C-Phe-Alg-CAD} \\ \\ \text{CH}_3 \end{array}$	197.0	11.7	17.00

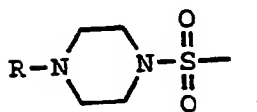
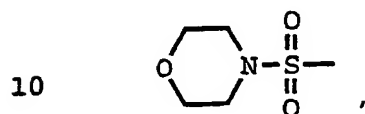
A method of preparing a compound having the
Formula I

A-E-G-J

5

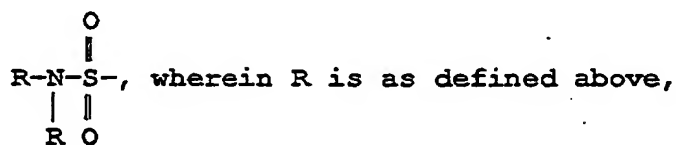
I

wherein A is

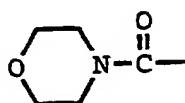


wherein R is hydrogen or alkyl of
from one to six carbon atoms,

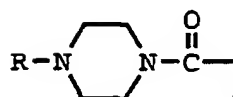
15



20

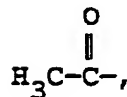


25

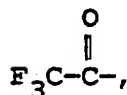


wherein R is as defined above,

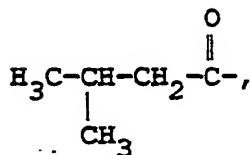
30

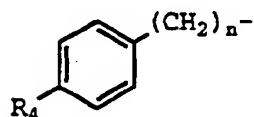
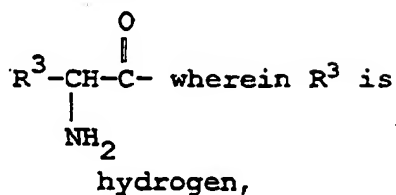
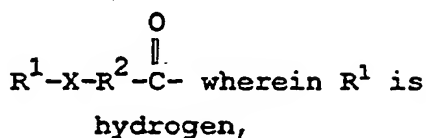
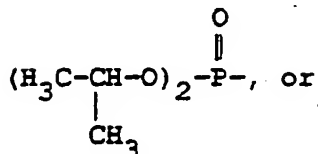
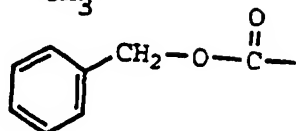
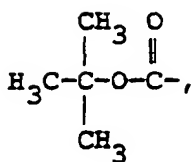


35

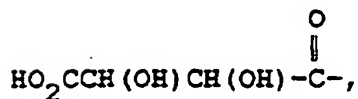
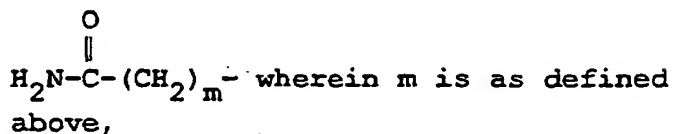
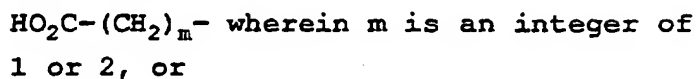
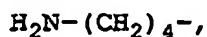


40

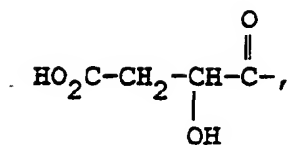




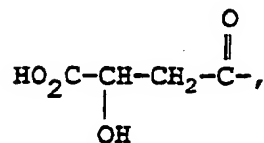
wherein n is zero or an integer of 1 or 2 and R^4 is hydrogen or hydroxyl,



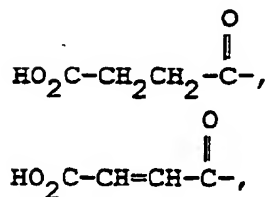
5



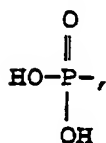
10



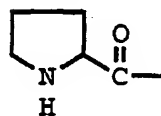
15



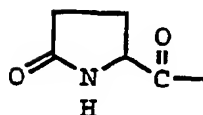
20



25



, or

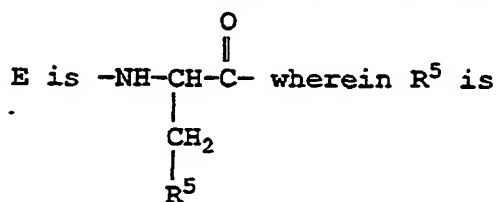


30

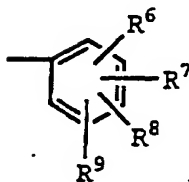
X is O, S, or NH, and

R² is alkyl of from one to six carbon atoms;

35



40

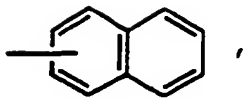


45

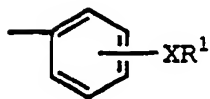
wherein R⁶, R⁷, R⁸, or R⁹ are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon

atoms, halogen, or
trifluoromethyl,

5

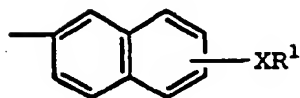


10



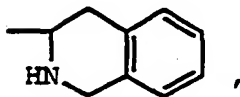
wherein R¹ and X are as
defined above,

15

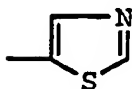


wherein R¹ and X are as
defined above,

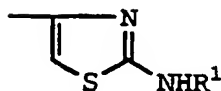
20



25

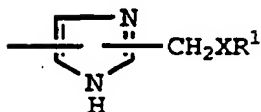


30



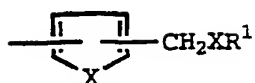
wherein R¹ is as defined
above,

35

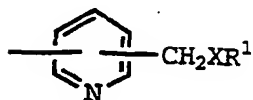


wherein X and R¹ are as
defined above,

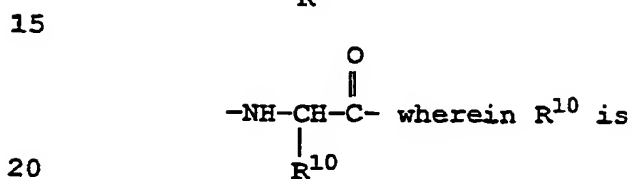
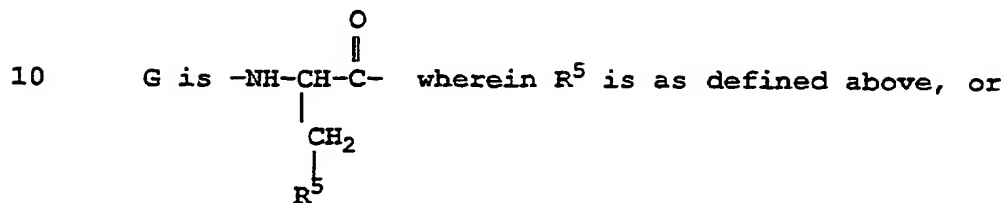
-44-



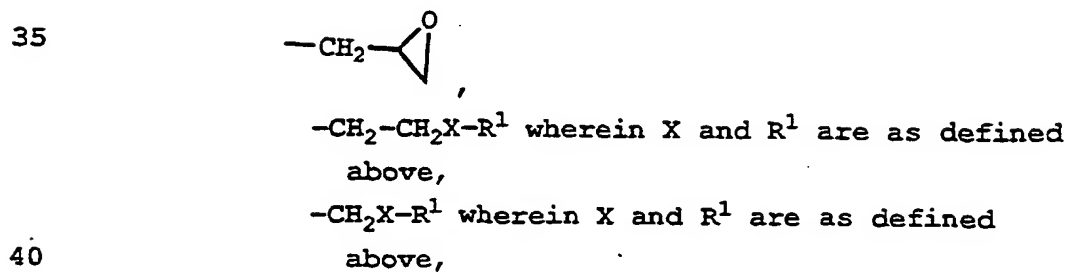
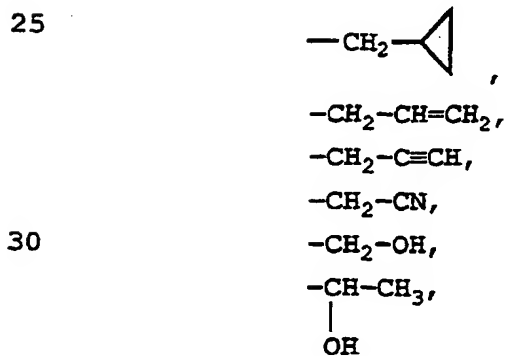
wherein R^1 and X are as defined above, or



wherein R^1 and X are as defined above;



hydrogen,
alkyl of from one to six carbon atoms,
 $\text{---CO}_2\text{CH}_3$,



-45-

-CHX-R¹ wherein X and R¹ are as defined



above,

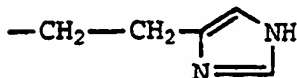
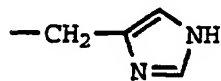
5

-CH₂-CH₂CH₂CH₂-NH₂,

-CH₂-CH₂-S(O)_n-R¹ wherein n and R¹ are as defined above,

-(CH₂)_n-CONH₂ wherein n is as defined above,

10

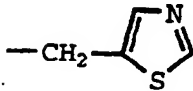


15



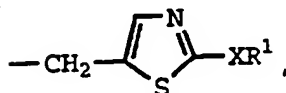
wherein R¹ is as defined above,

20



, or

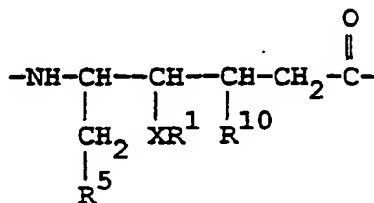
25



wherein X and R¹ are as defined above;

alternatively, E-G is

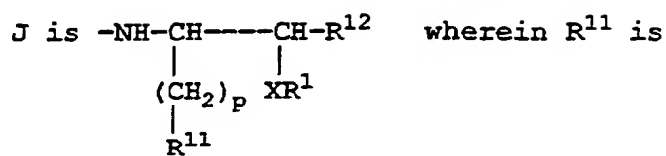
30



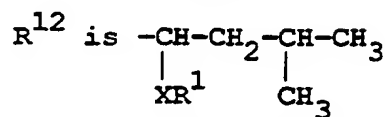
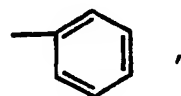
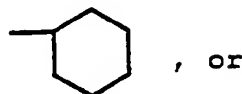
35

wherein R¹, X, R⁵, and R¹⁰ are as defined above;

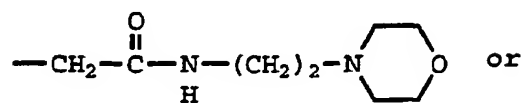
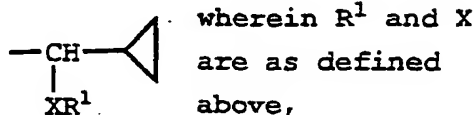
-46-



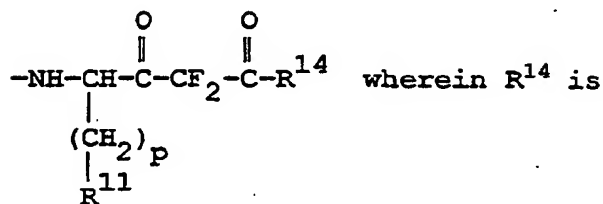
hydrogen,
alkyl,



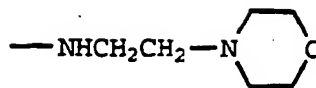
wherein R^1 and X are as
defined above,



$\text{--CH}_2\text{--OC}_2\text{H}_5$ and R^1 and X are as
defined above and p is zero or an
integer of one, or



-47-

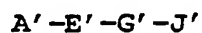


or



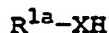
and R^{11} and p are as defined above;
provided R^1 with the exclusion of R^1 being hydrogen
is encompassed within the definition of at least one
of A, E, G, or J; or a pharmaceutically acceptable
salt thereof comprises:

a) coupling a compound of Formula II



II

wherein A' , E' , G' , and J' are as defined above for
A, E, G, and J provided R^1 is hydrogen and is
encompassed within the definition of at least
one of A' , E' , G' , or J' with a compound of
Formula III



III

wherein R^{1a} is as defined above for R^1 but
excluding R^1 is hydrogen and providing any basic
or acidic groups contain conventional protecting
groups and X is as defined above to afford a
compound of Formula IV



IV

wherein A'', E'', G'', and J'' are as defined above for A, E, G, and J provided R^{1a} is as defined above and is encompassed within the definition of at least one of A'', E'', G'' or J'';

b) a compound of Formula IV is deprotected in a conventional manner to afford a compound of Formula I; and if desired, converting a compound of Formula I to a corresponding pharmaceutically acceptable salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable salt to a compound of Formula I by conventional means.

A compound of Formula II may be prepared by sequential stepwise or fragment coupling of the amino acids or fragments selected from A', E', G', or J' to the preceding amino acid or fragment using conventional peptide synthesis methodology such as, for example, solution peptide synthesis or solid phase peptide synthesis to afford a compound of Formula II.

A compound of Formula IV is prepared from amino acids or fragments selected from A'', E'', G'', or J'' using the methodology used to prepare a compound of Formula II.

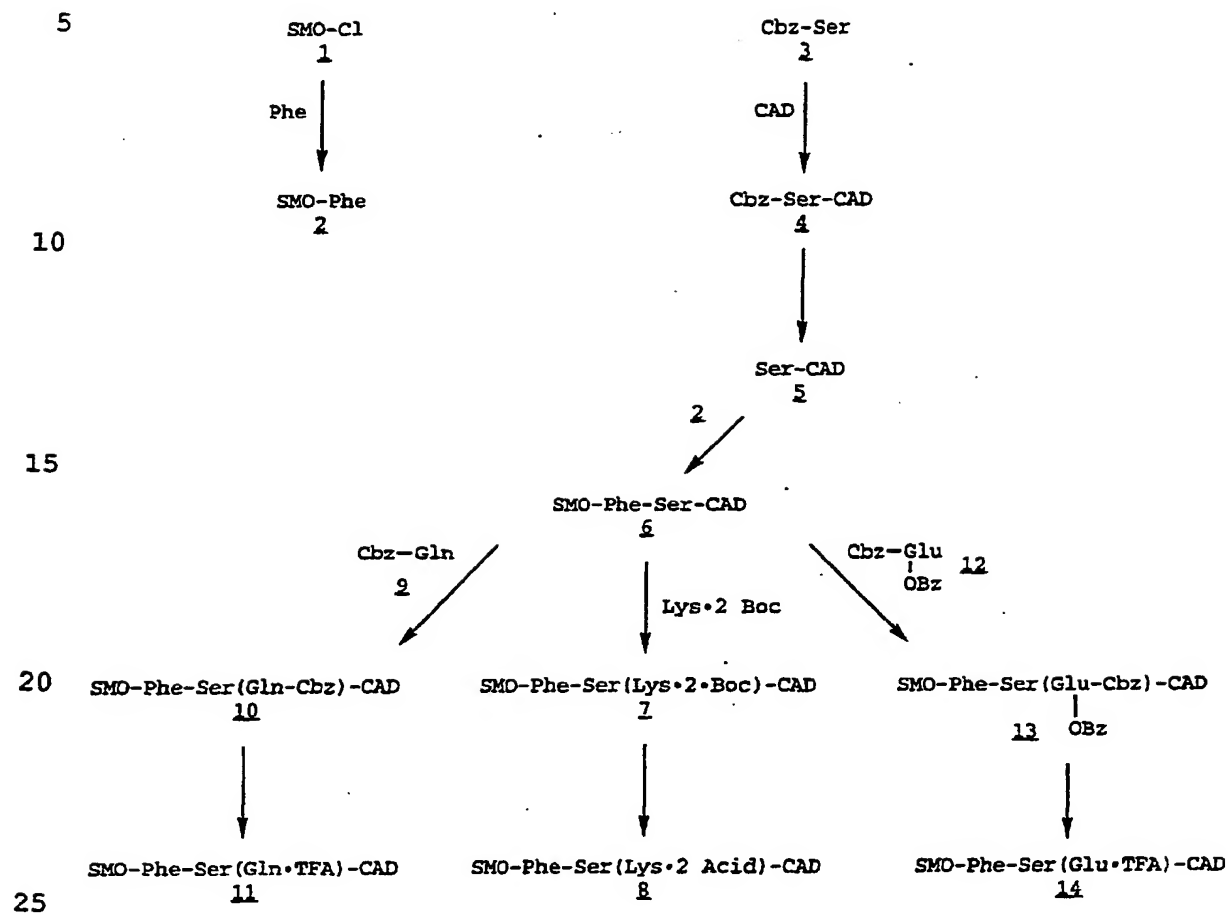
A compound of Formula III is either known or capable of being prepared by methods known in the art.

Coupling methods that can be employed in preparing the compounds of Formula I are discussed in "The Peptides. Analysis, Synthesis, Biology," Gross, E., and Meienhofer, J., eds. Academic Press, New York, New York, Vol. 1, 1979. Further, protecting groups that may be employed in the preparation of a compound of Formula I, as well as methods for incorporation and removal of these protecting groups are discussed in "The Peptides."

..Analysis, Synthesis, Biology," Gross, E., and
Meienhofer, J., eds., Academic Press, New York,
New York, Vol. 3, 1981.

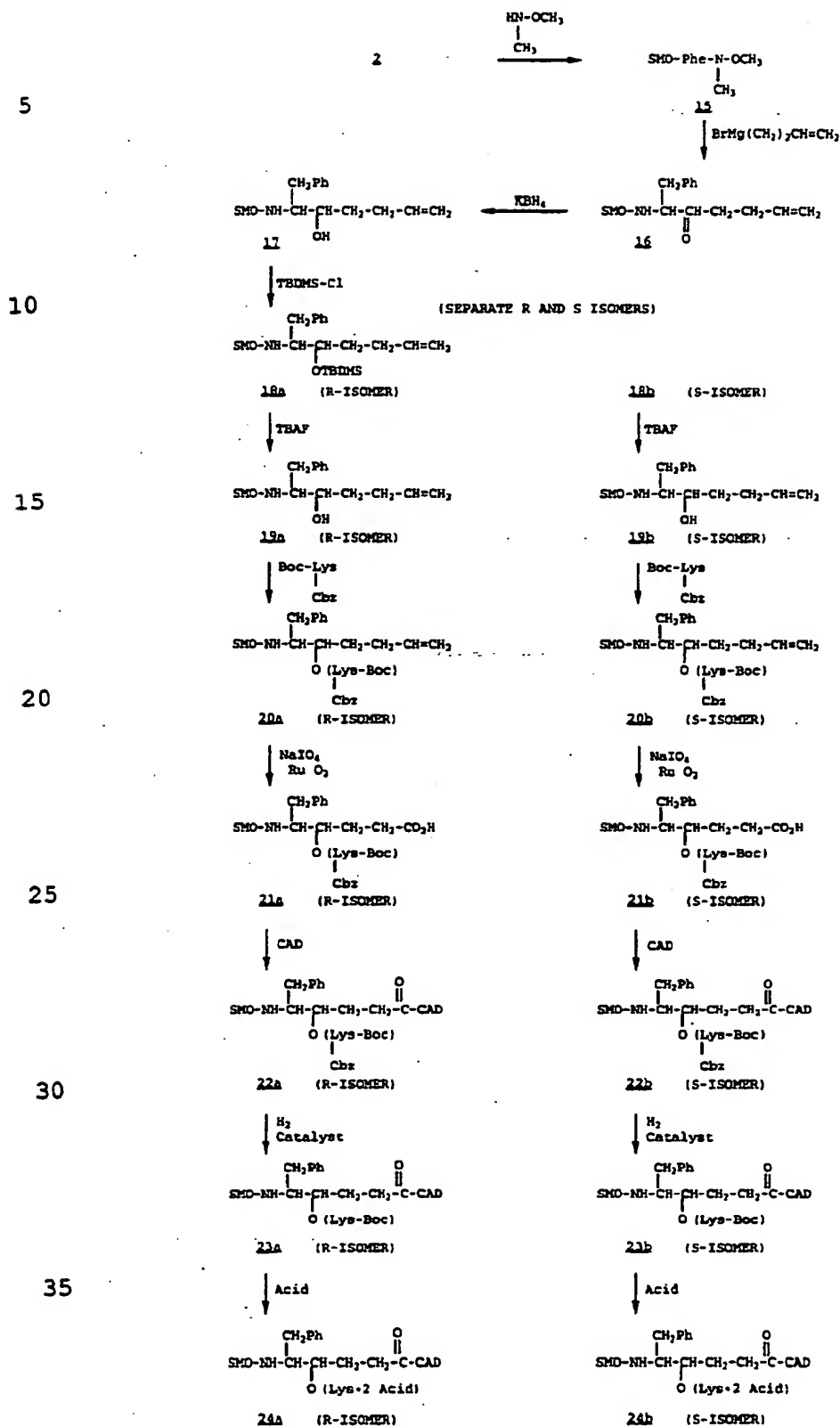
-50-

SCHEME 1



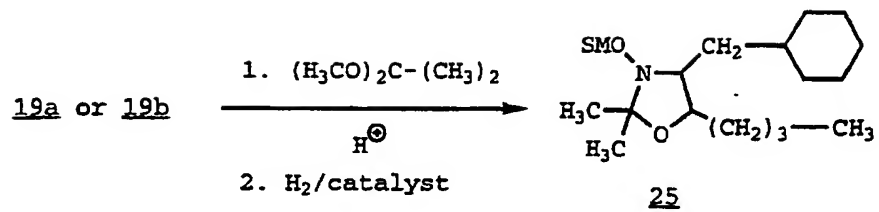
-51-

SCHEME 2



SCHEME 3

5



10

15

20

25

30

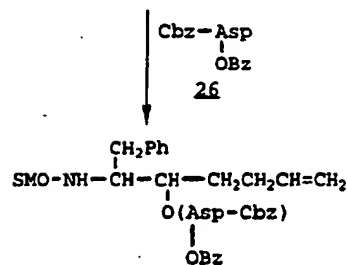
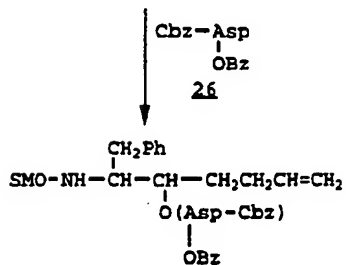
35

SCHEME 4

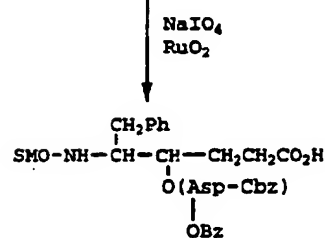
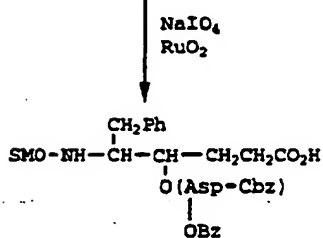
5

19a (R-isomer)**19b (S-isomer)**

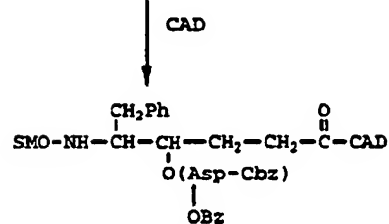
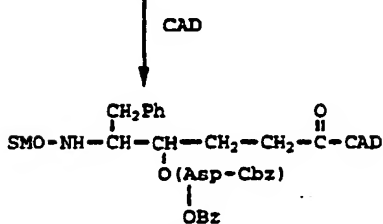
10

**(R-isomer)**
27a**(S-isomer)**
27b

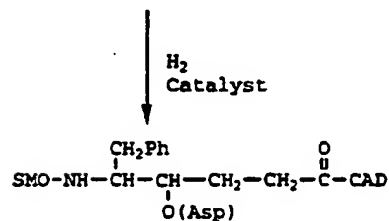
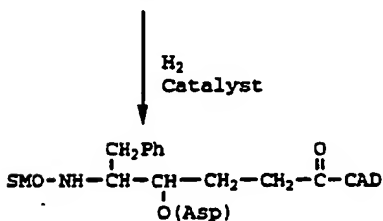
15

**(R-isomer)**
28a**(S-isomer)**
28b

20

**(R-isomer)**
29a**(S-isomer)**
29b

25

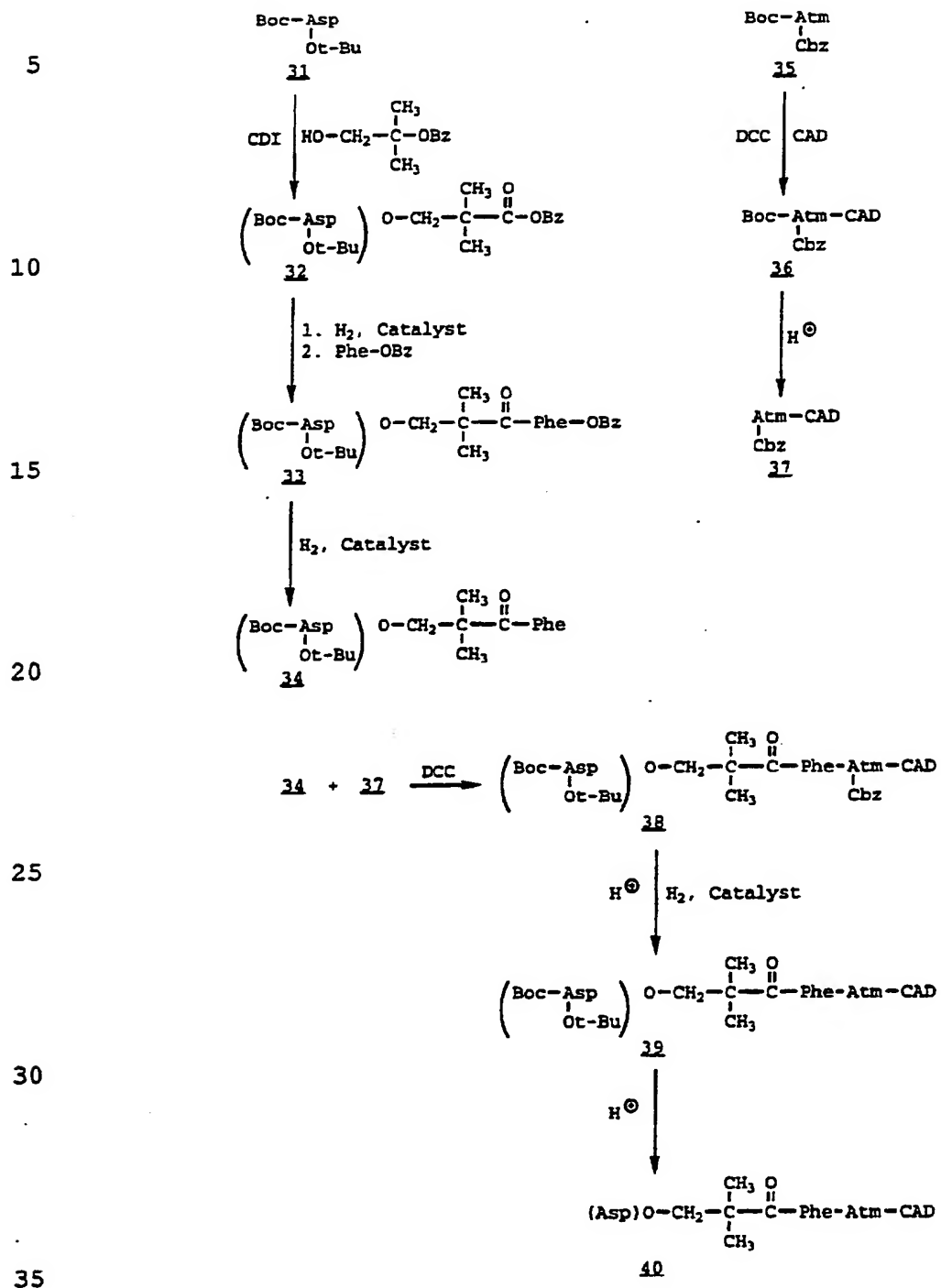
**(R-isomer)**
30a**(S-isomer)**
30b

30

35

-54-

SCHEME 5



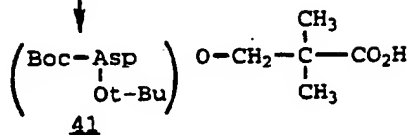
SCHEME 6

5

32

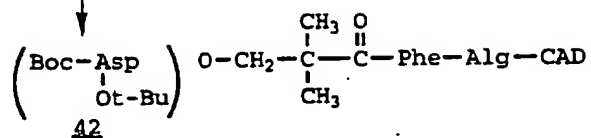
 H_2 , Catalyst

10

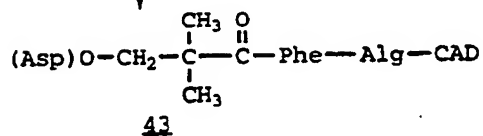


DCC Phe-Alg-CAD

15



20

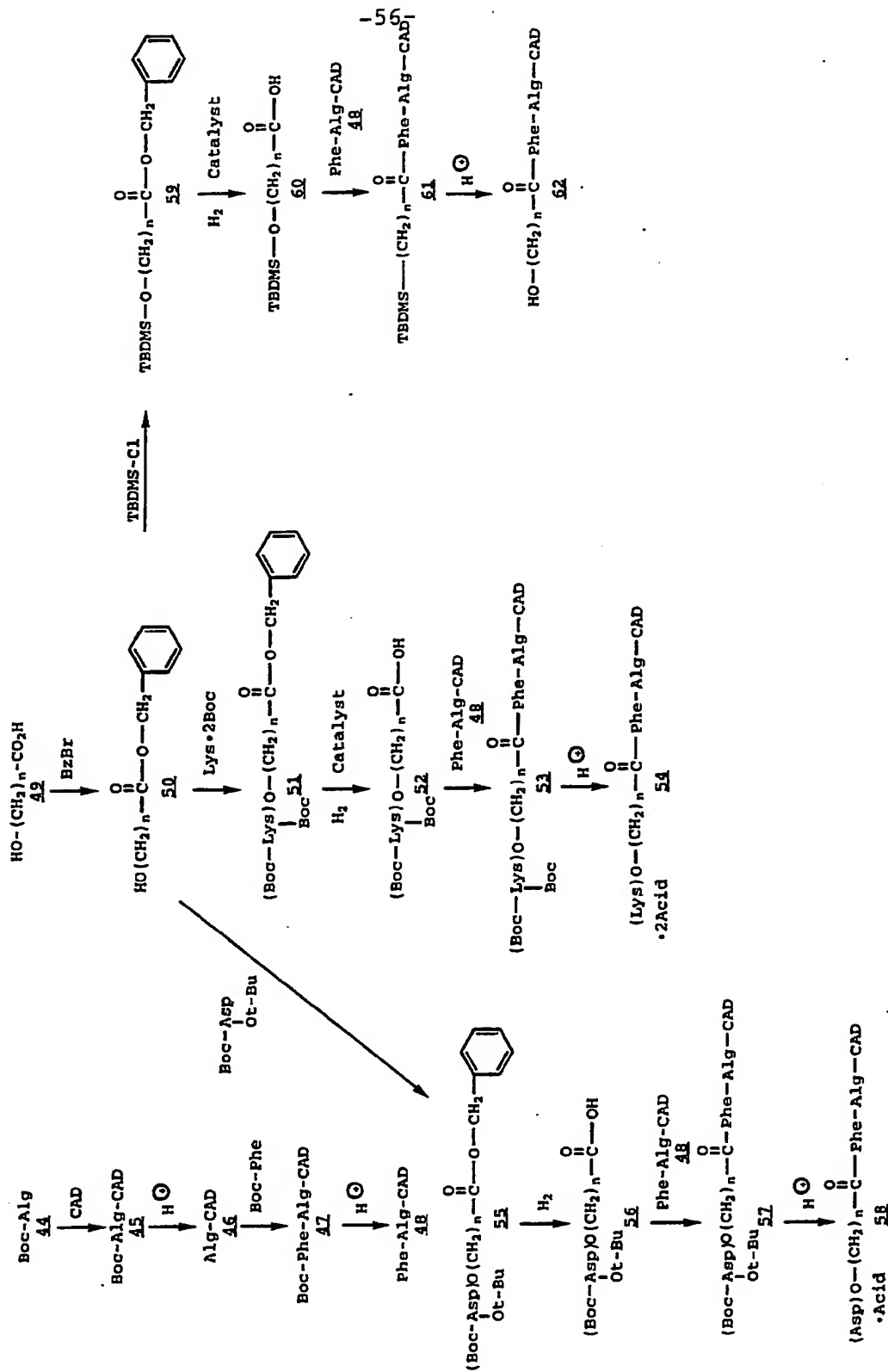
 H^+ 

25

30

35

SCHEME 7



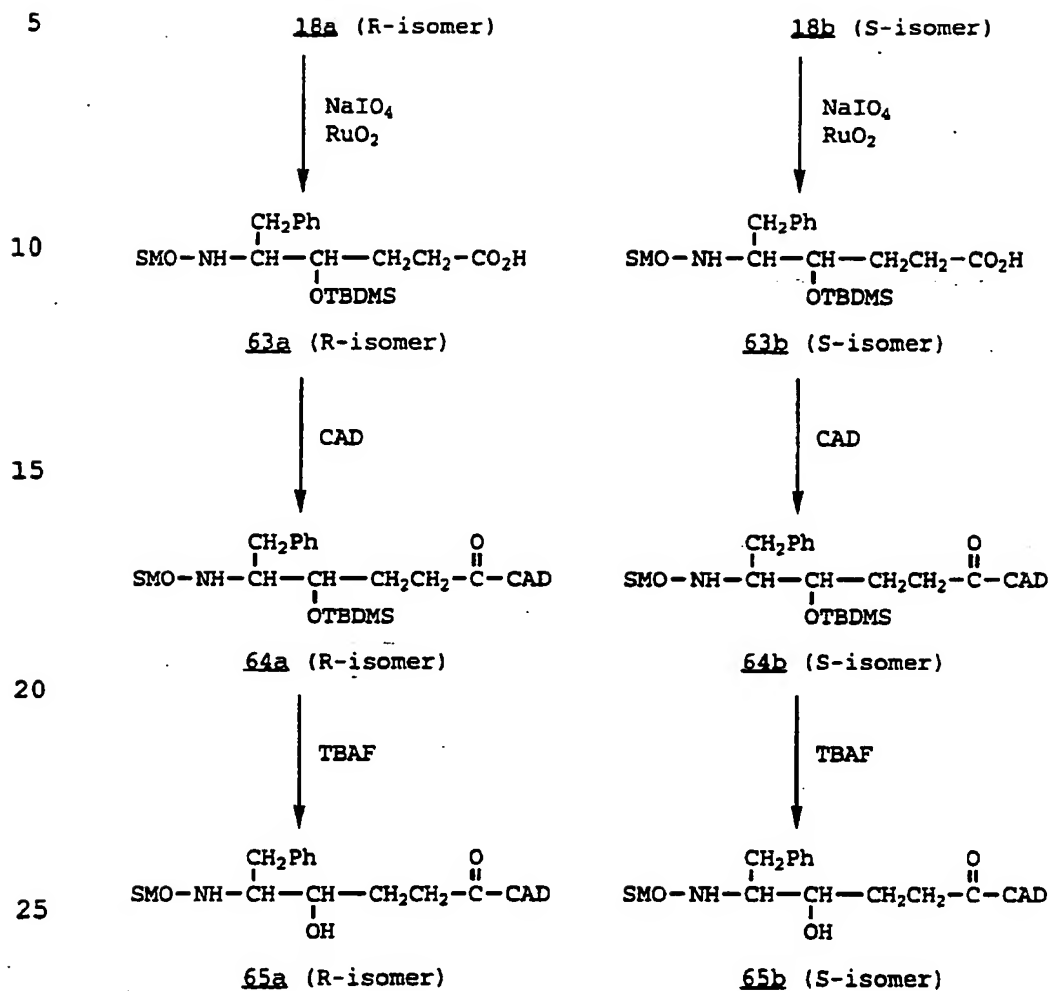
5

10

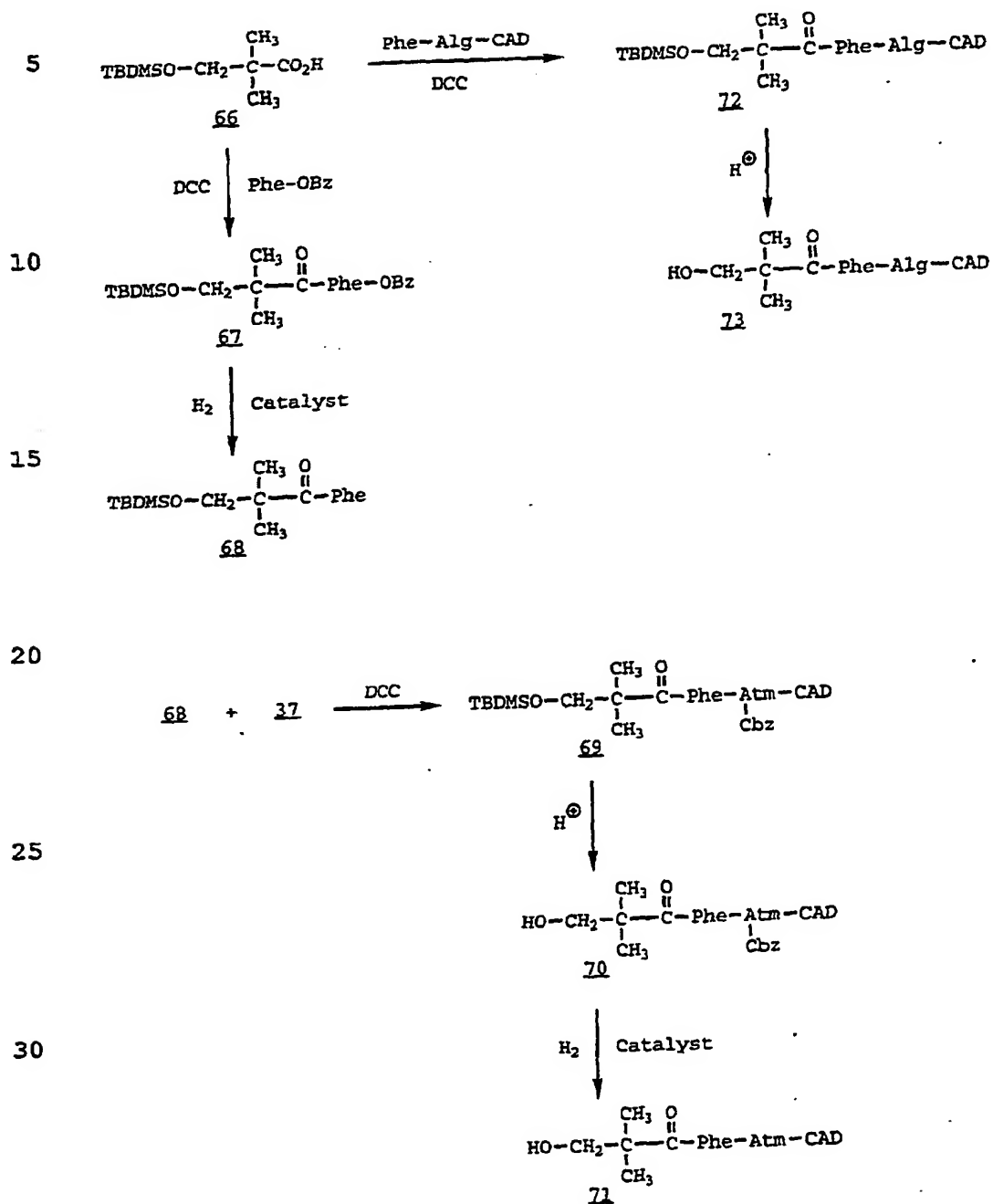
15

20

SCHEME 8



SCHEME 9



Preferred methods for the preparation of compounds of Formula I are described in Schemes 1 to 7.

Compounds of Formula I are designated by numbers 8, 11, 14, 24a, 24b, 30a, 30b, 40, 43, 54, and 58.

These schemes illustrate preferred methods from which a person, skilled in the art of organic chemistry, could analogously prepare all compounds of Formula I.

Compounds of Formula I designated 8, 11, and 14 are prepared from a compound of Formula 1 as outlined in Scheme I. Thus, SMO-Cl(1) (morpholinosulfamyl chloride) (prepared according to the method of R. Wegler and K. Bodenbenner, Annalen der Chemie, 624, 25 (1959)) is reacted with Phe in the presence of a base such as, for example, Et₃N and the like and a solvent such as, for example, CH₂Cl₂ and the like at about -30°C to about 100°C for about one to 24 hours to give the compound of Formula 2. Preferably, the reaction is carried out in the presence of Et₃N and CH₂Cl₂ at about 25°C for about 2 to 6 hours. Treatment of Cbz-Ser (3) with CAD in the presence of a coupling reagent such as, for example, DCC and HOBT and the like and a solvent such as, for example, CH₂Cl₂, CHCl₃, THF and the like optionally in the presence of an aprotic solvent such as, for example, DMF, DMSO and the like at about 0°C to about 25°C for about 6 hours to about 5 days to give the compound of Formula 4. The compound of Formula 4 is treated with hydrogen in the presence of a catalyst such as, for example, 5% to 20% palladium on carbon, platinum oxide, 5% to 20% platinum on carbon, and the like in a solvent such as, for example, EtOH, EtOAc, THF, dioxane, DMF and the like at about 0°C to about 100°C for about 30 minutes to about 24 hours to give the compound of Formula 5. The compound of Formula 2 is reacted with the compound of Formula 5 in the

presence of a coupling reagent such as, for example, DCC and HOBT and the like and a solvent such as, for example, CHCl_3 , CH_2Cl_2 , THF, dioxane, EtOAc, DMF, DMSO and the like at about 0°C to about 40°C for about 1 to 5 days to give the compound of Formula 6. The compound of Formula 6 is reacted with LYS.2BOC in the presence of a coupling reagent such as, for example, CDI, DCC, and the like in the presence of a solvent such as, for example, CHCl_3 , CH_2Cl_2 , THF, dioxane, EtOAc, DMF, DMSO and the like at about 0°C to about 100°C for about 3 hours to about 3 days to give the compound of Formula 7. The compound of Formula 7 is treated with an acid such as, for example, trifluoroacetic acid, or a nonpolar inert solvent such as CH_2Cl_2 saturated with hydrogen chloride gas at about -20°C to about 25°C for about 1 to 5 hours to give the compound of Formula 8.

In a similar manner the compound of Formula 6 is reacted with Cbz-Gln or Cbz-Glu to afford,

20

OBz

respectively, a compound of Formula 10 and a compound of Formula 13. Compounds of Formula 10 and 13 are reacted with hydrogen in the presence of a catalyst such as for example 50% palladium on carbon and an acid such as for example TFA and the like in a solvent such as for example ethanol and the like to afford, respectively, a compound of Formula 11 and a compound of Formula 14.

30

Compounds of Formula I designated 24a and 24b are prepared from a compound of Formula 2 as outlined in Scheme 2. Thus, the compound of Formula 2 is reacted with a coupling reagent such as, for example, CDI and the like in a solvent such as THF, CH_2Cl_2 , mixtures thereof and the like followed by O,N-dimethylhydroxylamine hydrochloride and a base such as, for example, N-methylpiperidine and the like to give the compound of Formula 15. The compound of

35

Formula 15 is added to the magnesium Grignard reagent of 4-bromo-1-butene in a solvent such as, for example, THF, Et₂O and the like to give the compound of Formula 16. The compound of Formula 16 is treated with a hydride reagent such as, for example, KBH₄ and the like in a solvent such as, for example, absolute EtOH and the like to give the compound of Formula 17 as a mixture of R and S isomers at the carbon atom to which the hydroxyl group is attached. Choice of solvent and reducing reagent can vary the ratio of isomers obtained to give a predominant excess of a particular desired isomer. The R and S isomers of the compound of Formula 17 may be separated into the individual R and S isomers by conventional separation techniques such as, for example, chromatography, fractional crystallization and the like. Alternatively, the compound of Formula 17 (R and S mixture of isomers) is reacted with t-butyldimethylsilyl chloride (TBDMS-Cl) in the presence of imidazole and DMF to give the compound of Formula 18 as a mixture of R and S isomers at the carbon atom to which the O-TBDMS group is attached. The R and S isomers of the compound of Formula 18 may be separated into the individual R and S isomers by conventional separation techniques such as, for example, chromatography and the like. Additionally, other hydroxyl protecting groups such as, for example, acetyl, benzyl, and the like may be used in place of the TBDMS group with subsequent separation of the R and S protected hydroxyl groups following the methodology used to separate the isomers of the compound of Formula 18. Either the compound of Formula 18a (R-isomer) or Formula 18b (S-isomer) is reacted with a fluoride ion source such as, for example, t-butylammonium fluoride and the like in a solvent such as, for example, THF and the like to give the compound of Formula 19a (R-isomer) or

Formula 19b (S-isomer). Either the compound of Formula 19a (R-isomer) or Formula 19b (S-isomer) is reacted with the imidazolide of N- α -Boc- ϵ -CBZ-LYS (prepared from N α -Boc- ϵ -Cbz-Lys, CDI and DMAP) (optionally compatible N-protecting groups other than Boc or Cbz may also be used to protect the amino groups of Lys) in a solvent such as, for example, CH₂Cl₂ and the like at about ambient temperature to give the compound of Formula 20a (R-isomer) or Formula 20b (S-isomer). Either the compound of Formula 20a (R-isomer) or Formula 20b (S-isomer) is treated with an oxidizing reagent such as, for example, NaIO₄ with a catalytic amount of RuO₂, and the like to give the compound of Formula 21a (R-isomer) or Formula 21b (S-isomer). Either the compound of Formula 21a (R-isomer) or Formula 21b (S-isomer) is reacted with CAD in the presence of a coupling reagent such as, for example, DCC and HOBT and the like in a solvent such as, for example, CH₂Cl₂, CHCl₃, THF and the like, optionally an aprotic solvent such as, for example, DMF, DMSO and the like is added to aid solution, at about 0°C to about 25°C for about 4 hours to about 3 days to give the compound of Formula 22a (R-isomer) or Formula 22b (S-isomer). Either the compound of Formula 22a (R-isomer) or Formula 22b (S-isomer) is treated with hydrogen in the presence of a catalyst such as, for example, 5% to 20% palladium on carbon, platinum oxide, 5% to 20% platinum on carbon, platinum oxide, 5% to 20% platinum on carbon, and the like in a solvent such as, for example, EtOH and the like to give the compound of Formula 23a (R-isomer) or Formula 23b (S-isomer). Either the compound of Formula 23a (R-isomer) or Formula 23b (S-isomer) is treated with an acid such as, for example, trifluoroacetic acid, a nonpolar inert solvent such as, for example, CH₂Cl₂ and the like saturated with

hydrogen chloride gas to give the compound of
Formula 24a (R-isomer) or Formula 24b (S-isomer) as
the diacid addition salt. The diacid addition salt
of the compound of Formula 24a (R-isomer) or
5 Formula 24b (S-isomer) may be converted to other
pharmaceutically acceptable acid addition salts by
conventional methodology as previously described.
The configuration of each isomer at the carbon atom
to which the hydroxyl or derivatized hydroxyl group
10 is attached is assigned as outlined in Scheme 3.
Thus, either the compound of Formula 19a or
Formula 19b is reacted with 2,2-dimethoxypropane in
the presence of an acid catalyst such as, for
example, para-toluenesulfonic acid and the like
15 followed by reduction with hydrogen in the presence
of a catalyst such as, for example, rhodium on carbon
and the like to afford the compound of Formula 25a or
Formula 25b. ¹H-NMR decoupling determinations
indicate the stereochemistry of the protons attached
20 to the five-membered ring.

Compounds of Formula I designated 30a and 30b
are prepared, respectively, from a compound of
Formula 19a and 19b as outlined in Scheme 4 using the
methodology used to prepare compounds of Formula 24a
25 and 24b from compounds of Formula 19a and 19b as
described in Scheme 2.

A compound of Formula I designated as 40 is
prepared from a compound of Formula 31 as outlined in
Scheme 5.

30 A compound of Formula I designated as 43 is
prepared from a compound of Formula 32 as outlined in
Scheme 6.

Compounds of Formula I designated 54 and 58 are
prepared respectively from a compound of Formula 49
35 and a compound of Formula 44 as outlined in Scheme 7.

The preparation of selected parent renin
inhibitors of compounds of Formula I designated as

65a, 65b, 71, and 73 are as outlined in Schemes 8 and 9.

5 The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

10 For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, 15 suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. 20

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

25 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, 30 magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as 35 a carrier providing a capsule in which the active

component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, 5 cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is 10 dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, 15 suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be 20 prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active 25 component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which 30 are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, 35 stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsules, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 2000 mg preferably 0.5 mg to 1000 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents for treating hypertension, hyperaldosteronism, congestive heart failure, and diseases caused by retroviruses including HTLV I, II, and III as well as diagnostic tools for the identification of cases of hypertension due to renin excess, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.1 mg to about 50 mg per kilogram daily. A daily dose range of about 0.5 mg to about 30 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the

total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

SMO-Phe-Ser(Lys·2HCl)-CAD

Step A: Preparation of SMO-Phe-Ser(Lys·2 Boc)-CAD

Di-t-Boc-Lys (1.11 g, 3.19 mmol, 2.0 eq) in THF (7 mL) is added to CDI (570 mg, 3.51 mmol, 2.2 eq) in THF (7 mL) at 0°C under N₂ and stirred for 30 minutes. SMO-Phe-Ser-CAD (Example C) (1.0 g, 1.60 mmol) in THF (5 mL) is added and the mixture stirred at room temperature for 3 days. The solvents are evaporated and the residue partitioned between ethyl acetate (50 mL) and 2N HCl (50 mL). The organic layer is separated, washed with 2N sodium carbonate (50 mL), brine (50 mL), dried (MgSO₄), filtered and evaporated to afford a white foam. This is purified by column chromatography on silica gel eluting with 2% then 3% MeOH/CH₂Cl₂ to give a white foam. This is further purified by column chromatography on silica gel (thin layer chromatography - TLC grade) eluting with 3% methanol/dichloromethane to give 699 mg of a white foam.

¹H NMR (300 MHz, d⁶DMSO + 2 drops D₂O) δ 8.56 (1H, d, J = 9Hz), 7.69 (1H, d, J = 10 Hz), 7.10-7.40 (6 H, m), 6.72 (1H, br t), 4.61 (1H, m), 4.10-4.30 (3H, m), 3.95 (2H, m), 3.35 (4H, m), 3.41 (1H, t, J = 9 Hz), 2.80-3.00 (4H, m), 2.55-2.75 (5 H, m), 1.00-1.80 (40H, m), 0.86 (3H, d, J = 7.2 Hz), 0.78 (3H, d, J = 7.0 Hz).

Step B: Preparation of SMO-Phe-Ser(Lys·2 HCl)-CAD

SMO-Phe-Ser(Lys·2Boc)-CAD (600 mg, 0.628 mmol) in CH₂Cl₂ (5 mL) is added to CH₂Cl₂ (20 mL) saturated with HCl (gas) at 0°C and stirred at 0°C for 2 hours.

5 The solvents are evaporated and the residue taken up in water (30 mL) and washed with chloroform (3 x 20 mL). The water layer is filtered through 'hyflo' and freeze-dried to give 425 mg of a white powder. Mass spectrum-fast atom bombardment (MS

10 (FAB)) 755.2 (100%) - free base M⁺

EXAMPLE 2**SMO-Phe-Ser(Asp·HCl)-CAD**

15 **Step A: Preparation of SMO-Phe-Ser(Asp·Boc·t-Bu)-CAD**

γ-t-Bu(N-Boc) aspartate dicyclohexylammonium salt (1.50 g, 3.19 mmol, 4 eq) is added to 5% citric acid (100 mL) and extracted with ethyl acetate (3 x 50 mL), the extracts are washed with brine

20 (100 mL), dried (MgSO₄), filtered and evaporated to an oil. This is dissolved in THF (5 mL) and added to CDI (569 mg, 3.51 mmol, 4.4 eq) at 0°C and stirred for 1 hour. Smo-Phe-Ser-CAD (Example C) (0.5 g, 0.80 mmol) in THF (2 mL) is added and the mixture

25 stirred for 1 week. The mixture is diluted with EtOAc (30 mL), washed with 5% citric acid solution (50 mL), 2 N Na₂CO₃ (50 mL), brine (50 mL), dried (MgSO₄), filtered and evaporated to leave a brown solid. This is purified by column chromatography (2% to 3% MeOH/CH₂Cl₂) to afford the product as white

30 foam (573 mg). Further chromatography (2% MeOH/CH₂Cl₂, TLC silica) affords 277 mg of a white solid. ¹H NMR (300 MHz, d⁶-DMSO + 2 drops D₂O) δ 7.20-7.40 (6H, m), 4.62 (1H, t, J = 5.8 Hz),

35 4.40 (1H, dd, J = 9.7, 3.5 Hz), 4.10-4.30 (3H, m), 3.94 (1H, dd, J = 11.2, 3.3 Hz), 3.34 (4H, br s), 3.06 (1H, t, J = 5.2 Hz), 2.85-3.00 (2H, m), 2.40-

2.75 (8H, m), 1.00-1.80 (34H, m), 0.84 (3H, d, $J = 6.7$ Hz), 0.78 (3H, d, $J = 6.4$ Hz).

Step B: Preparation of SMO-Phe-Ser(Asp·HCl)-CAD

5 Hydrogen chloride gas is passed over the aspartate (588 mg, 0.65 mmol) in CH_2Cl_2 (20 mL) at room temperature and stirred for 1 hour. The solvent is evaporated and the residue dissolved in CHCl_3 . This is evaporated to leave a white solid. This is
10 dissolved in water (150 mL) and washed with EtOAc (100 mL). Hexane (50 mL) is added to break down the emulsion that forms and the aqueous layer filtered through celite and evaporated to afford 447 mg of a white solid. ^1H NMR (200 MHz, $\text{d}^6\text{-DMSO} + 2$ drops D_2O)
15 7.20-7.40 (6H, m), 4.91 (1H, t, $J = 5.0$ Hz), 4.82 (1H, d, $J = 6.0$ Hz), 4.46 (2H, m), 4.12 (1H, brt, $J = 5.0$ Hz), 3.69 (1H, brm), 3.34 (4H, br s), 2.50-3.10 (11H, m), 1.00-1.80 (15H, m), 0.95 (3H, d, $J = 7.0$ Hz).

20

EXAMPLE 3

SMO-Phe-Thr(Lys·2HCl)-CAD

Step A: Preparation of SMO-Phe-Thr(Lys·2Boc)-CAD

25 Di-t-Boc-Lys (5.41 g, 15.6 mmol, 5 eq) in THF (20 mL) is added to CDI (3.04 g, 18.7 mmol, 6 eq) in THF (20 mL) at 0°C under N_2 . After stirring at 0°C for 5 min, the solution becomes homogenous. TLC confirmed no lysine present. SMO-Phe-Thr-CAD
30 (Example D) (1.926 g, 3.00 mmol) in THF (20 mL) and DMAP (100 mg) are added at 0°C . The mixture is stirred at room temperature overnight and then at reflux for 24 hours. The cooled mixture is evaporated, the residue taken up in EtOAc (300 mL),
35 washed with 2 N HCl (200 mL), 2 N Na_2CO_3 (200 mL), brine (200 mL), dried (MgSO_4), filtered and evaporated to leave a white foam (~8 g). This is

purified by column chromatography on silica gel (flash) eluting with 2% then 3% MeOH/CH₂Cl₂ to give a white foam (2.93 g). This is further purified by column chromatography twice on silica gel (2 x 100 g TLC grade) to afford 578 mg of a white foam. HPLC 98.6% pure.

Step B: Preparation of SMO-Phe-Thr(Lys·2HCl)-CAD

The lysine ester (600 mg) in CH₂Cl₂ (5 mL) is added to saturated HCl/CH₂Cl₂ (20 mL) at 0°C and the mixture stirred at room temperature for 4 hours. The solvent is evaporated to leave the product as an off-white solid. This is dissolved in water (50 mL) and washed with EtOAc (50 mL), filtered through celite and freeze-dried to afford 454 mg of a fluffy white solid. MS (FAB) 769.5 (17%) M⁺ of free base.

EXAMPLE 4

SMO-Phe-Ser(Glu·TFA)-CAD

Step A: Preparation of SMO-Phe-Ser(Glu·Cbz)-CAD

OBz

A mixture of SMO-Phe-Ser-CAD (Example C) (300 mg, 0.479 mmol), Glu·Cbz·Bz (178 mg, 0.479 mmol), DDC (99 mg, 0.479 mmol), and DMAP (12 mg, 95.7 μmol) in dichloromethane (5 mL) is stirred at room temperature for 16 hours. The mixture is filtered and evaporated to leave an oil. The oil is purified by column chromatography on silica gel (50 g TLC grade) eluting with 2% methanol/dichloromethane to give 347 mg of a white solid; MS (FAB) 980.6 (42%) M⁺.

Step B: Preparation of SMO-Phe-Ser(Glu·TFA)-CAD

SMO-Phe-Ser(Glu·Cbz)-CAD (340 mg, 0.347 mmol) is

OBz

stirred in ethanol (20 mL) with 5% palladium on carbon (120 mg) and TFA (134 μL, 1.73 mmol) under

hydrogen. After 6 hours the mixture is filtered through hyflo and evaporated to leave an oil. This oil is dissolved in water (50 mL) and ethanol (30 mL), filtered through hyflo, and evaporated to remove the ethanol. The remaining aqueous phase is freeze-dried to give a white solid. This solid is dried to 50°C under high vacuum to give 277 mg of a white solid; MS (FAB) 756.5 (100%) M+.

10

EXAMPLE 5

SMO-Phe-Ser(Gln·TFA)-CAD

Step A: Preparation of SMO-Phe-Ser(Gln·Cbz)-CAD

SMO-Phe-Ser-CAD (Example C) (300 mg, 0.479 mmol) is reacted with Gln·Cbz (134 mg, 0.479 mmol) under the same conditions in Example 4, Step A to give 392 mg of a colorless oil;

¹H NMR (300 MHz, d⁶-DMSO + two drops D₂O):

δ 7.15-7.50 (11H, m), 5.01 (2H, s), 4.65 (1H, t, J = 6.1 Hz), 3.90-4.35 (5H, m), 3.35 (4H, s), 3.11 (1H, t, J = 9.2 Hz), 2.95 (2H, m), 2.15 (2H, t, J = 7.3 Hz), 0.95-2.05 (18H, m), 0.83 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.2 Hz).

20

Step B: Preparation of SMO-Phe-Ser(Gln·TFA)-CAD

SMO-Phe-Ser(Gln·Cbz)-CAD (305 mg, 0.343 mmol) is reacted under the same conditions in Example 4, Step B to give 252 mg of a white powder;

¹H NMR (300 MHz, d⁶-DMSO + two drops D₂O): δ 8.67 (1H, d, J = 7.9 Hz), 7.72 (1H, d, J = 9.2 Hz), 7.15-7.40 (6H, m), 4.72 (1H, q, J = 6.7 Hz), 3.85-4.40 (5H, m), 3.34 (4H, s), 2.95-3.15 (3H, m), 2.45-2.75 (6H, m), 2.27 (2H, m), 2.02 (2H, m), 0.95-1.85 (15H, m), 0.86 (3H, d, J = 6.6 Hz), 0.79 (3H, d, J = 6.6 Hz).

30

35

EXAMPLE 6

SMO-Phe-Ser(Ala·TFA)-CAD

Step A: Preparation of SMO-Phe-Ser(Ala-Cbz)-CAD

A mixture of SMO-Phe-Ser-CAD (Example C)
5 (300 mg, 0.468 mmol), Cbz-Ala (105 mg, 0.468 mmol,
1.0 eq), DCC (97 mg, 0.468 mmol, 1.0 eq) and DMAP
(11 mg, 94 μ mol, 0.2 eq) in dichloromethane (10 mL)
is stirred at room temperature for 16 hours. The
mixture is filtered and evaporated. The residue is
10 purified by column chromatography on silica gel (50 g
TLC grade) eluting with 2% methanol in
dichloromethane to give 407 mg of a colorless oil; MS
(FAB) 832.2 (36%) M^+ .

15 Step B: Preparation of SMO-Phe-Ser(Ala·TFA)-CAD

A mixture of SMO-Phe-Ser(Ala-Cbz)-CAD (349 mg,
0.419 mmol), 5% palladium on carbon (100 mg) and
trifluoroacetic acid (162 μ L, 5 eq) in ethanol
(50 mL) is stirred under hydrogen for 4 hours. The
mixture is filtered through 'Hyflo' (diatomaceous
20 earth) and evaporated to a white residue. This is
dissolved in 1:1 ethanol:water (100 mL), filtered
through 'Hyflo' and evaporated until all of the
ethanol has gone. The residue is freeze-dried to
25 afford a white powder (292 mg); MS (FAB) 698.2 (100%)
 M^+ of free base.

EXAMPLE 7

SMO-Phe-Mal-CAD(2·COCH₂CH₂CO₂H)

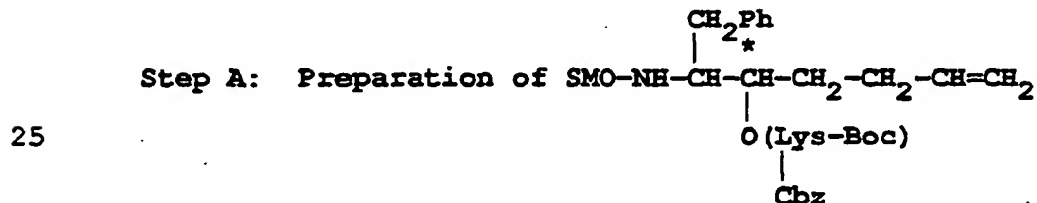
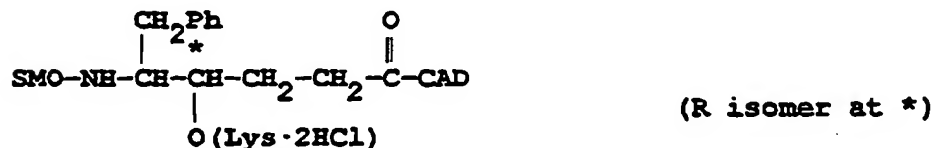
30 A mixture of SMO-Phe-Mal-CAD (U.S. 5,036,053)
(200 mg, 0.305 mmol), succinic anhydride (153 mg,
1.53 mmol, 5 eq) and DMAP (75 mg, 0.611 mmol, 2 eq)
is stirred in CH₂Cl₂ (2.5 mL) at room temperature for
2 days. The solvent is evaporated and the residue
35 taken up in EtOAc (30 mL) and washed with 2 N HCl
(2 x 20 mL). The EtOAc layer is washed with brine
(30 mL), dried (MgSO₄), filtered and evaporated to

-73-

leave a yellow foam. This is purified by column chromatography on silica gel eluting with 5% MeOH/0.5% HOAc/CH₂Cl₂ to afford 2.04 mg of a white foam.

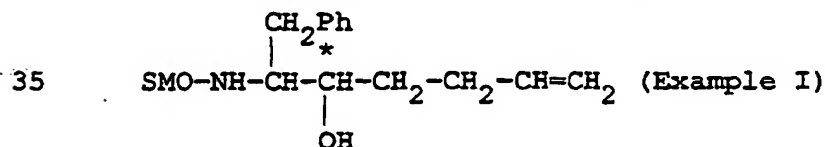
5 TLC silica gel plates (5% methanol/dichloromethane/1% HOAc) R_f 0.39; detection UV and phosphomolybdic acid. ¹H NMR (300 MHz, d⁶-DMSO) δ 12.15 (2H, brs), 8.87 (1H, 2 x d, J = 10.0 Hz), 8.31 (1H, d, J = 10.0 Hz), 7.73 (1H, t, J = 11.0 Hz), 7.15-7.50 (5H, m), 5.20 (1H, t, J = 9.0 Hz), 4.95 (2H, m), 4.20 (2H, m), 3.73 (3H, 2 x s), 3.03 (1H, m), 2.91 (1H, m), 2.35-2.75 (13H, m), 0.6-1.80 (21H, m).

15 EXAMPLE 8



(R isomer at *)

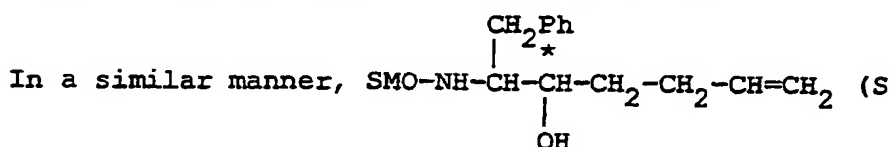
Alpha-Boc,epsilon-Cbz-Lys, 2.15 g (5.64 mmol), is dissolved in 75 mL dry dichloromethane and cooled to 5°C. CDI (1.05 g, 6.49 mmol), is added, and the mixture is warmed to 25°C over 1 hour.



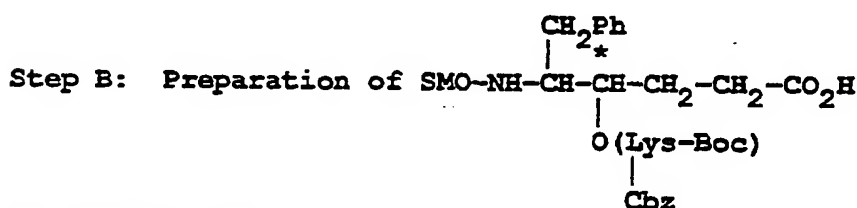
(R isomer at *), (2.0 g, 5.64 mmol) is dissolved in dichloromethane (50 mL), and is added to the previously prepared solution. A trace of DMAP is added, and the mixture is stirred at 25°C for 2 weeks. The mixture is then consecutively washed

40

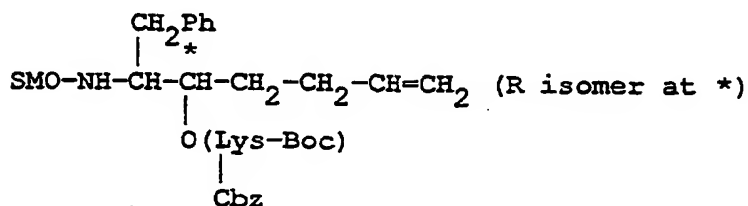
with 1N citric acid, saturated NaCl solution, saturated NaHCO₃ solution and saturated NaCl solution. The organic phase is dried over MgSO₄, filtered and evaporated under reduced pressure to afford a glassy solid, 4.02 g. Chromatography of the solid on silica gel eluting with EtOAc/hexane (25/75) gives the R isomer product as a white foam, 2.88 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 617.4 (100%) M⁺-Boc.



15 isomer at *) (2.0 g, 5.64 mmol) gives the desired S isomer product as a white foam, 2.65 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 617.4 (100%) M⁺-Boc.



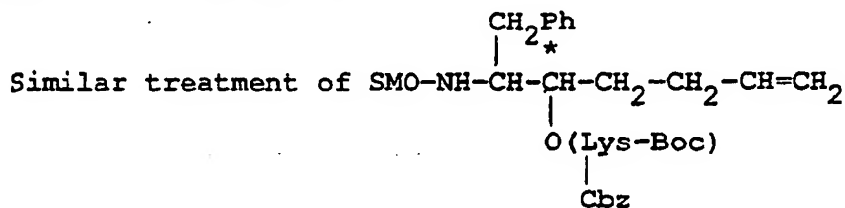
(R isomer at *)



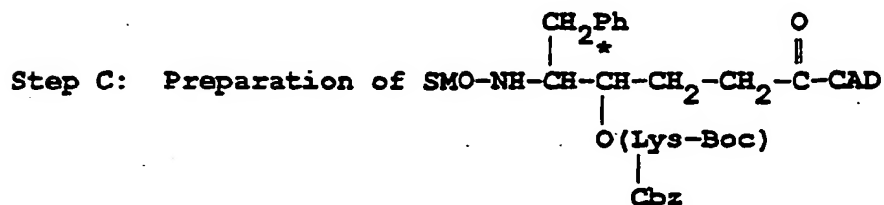
35 (2.66 g, 3.71 mmol) is dissolved in 100 mL acetone and cooled to 3°C. In a separate flask, NaIO₄ (5.52 g, 25.8 mmol) and ruthenium (IV) oxide hydrate (0.168 g) are dissolved in 65 mL H₂O. The solution is filtered and added to the previous solution, giving an exotherm to 28°C. Temperature is maintained by cooling at 25°C for 1.5 hours, after which isopropanol (5 mL) is added. After stirring for 15 minutes, the mixture is filtered, evaporated

40

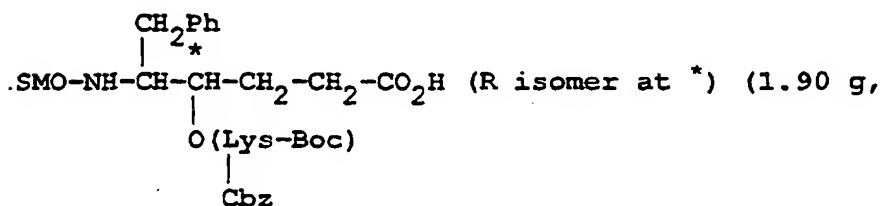
to an oily aqueous suspension, diluted with saturated NaCl solution and extracted into CHCl_3 . The organic extract is washed with a dilute Na_2SO_3 solution and the pH adjusted to 2.0 with 1 N HCl. The organic phase is washed with saturated NaCl solution, dried over MgSO_4 , filtered and evaporated to give the R isomer product as a white foam, 2.08 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 735.3 (4.65%) M^+ .



(S isomer at *), 2.48 g (3.46 mmol) gives the corresponding S isomer product as a white foam, 2.11 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 735.5 (3.8%) M^+ .



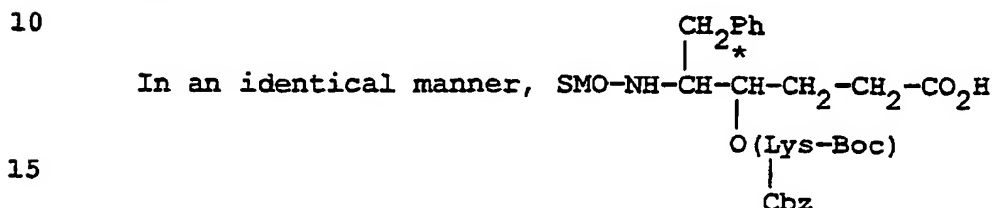
(R isomer at *)



is dissolved in dichloromethane (100 mL). A solution of HOBT (0.36 g, 2.66 mmol) in 5 mL DMF is added followed by a solution of CAD (0.63 g, 2.58 mmol) in dichloromethane (25 mL). The mixture is stirred and allowed to warm to 25°C overnight. The mixture is filtered and evaporated under reduced pressure. The residue is taken up into EtOAc and

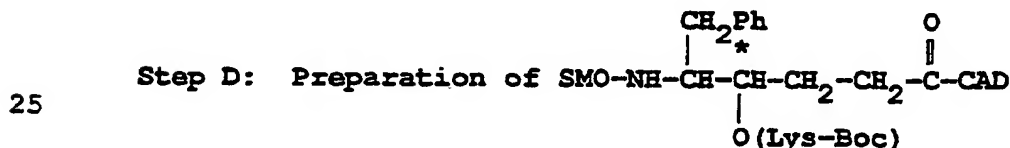
washed consecutively with solutions of saturated NaCl, 1 N citric acid, saturated NaHCO₃, and saturated NaCl. The organic phase is dried over MgSO₄, filtered, and evaporated to a foam, 2.61 g.

5 Chromatography on silica gel eluting with EtOAc/Hexane (40/60) gives the R isomer product as a white foam, 1.57 g. The structure is confirmed by NMR and Mass Spectroscopy. MS (FAB) 960.8 (14.3%) M⁺.

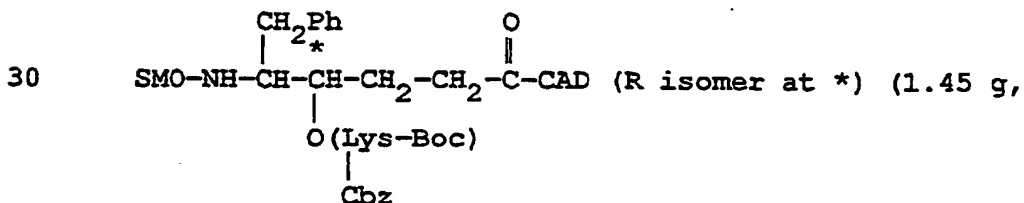


(S isomer at *) (1.90 g, 2.58 mmol), yielded 1.72 g of the corresponding S isomer product as a white foam. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 960.6 (15.1%) M⁺.

20



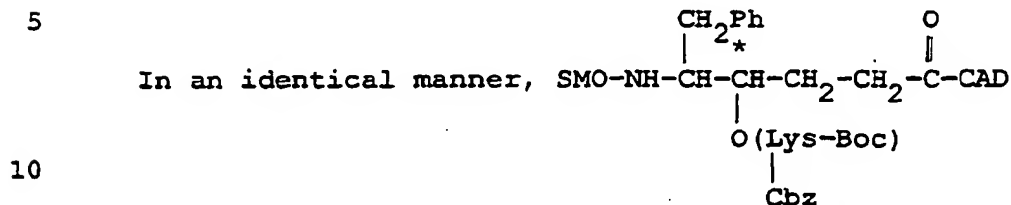
(R isomer at *)



35 1.51 mmol) is dissolved in methanol (100 mL) and 20% palladium on carbon catalyst (0.25 g) is added. The suspension is purged with H₂ gas for 3 hours, filtered, and evaporated under pressure to a white foam. The foam is dissolved in a minimal amount of dichloromethane and the resulting solution is added

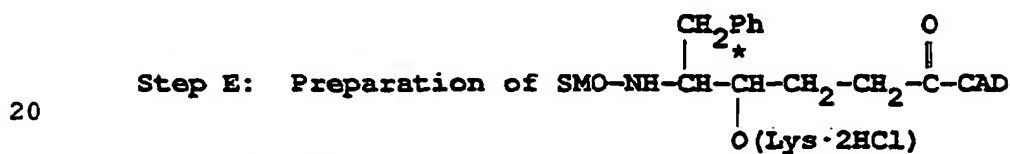
40 to Et₂O giving a solid precipitate. The solid is filtered, washed with Et₂O and dried in vacuo to give

0.94 g of the R isomer product as a white solid. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 826.7 (100%) M⁺.

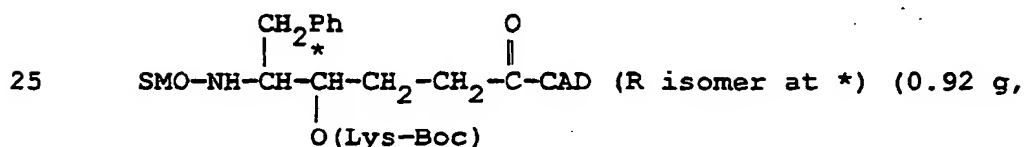


(S isomer at *) (1.60 g, 1.67 mmol) gives the S isomer product as a white solid, 1.07 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 826.7 (100%) M⁺.

15



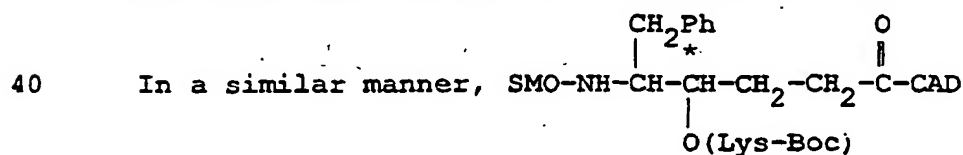
(R isomer at *)



1.11 mmol) is dissolved in 25 mL dichloromethane and occasionally purged with anhydrous HCl gas. After 1 hour, the mixture is evaporated under reduced pressure to a white solid. The solid is redissolved in dichloromethane, filtered, and the filtrate is added to Et₂O giving a solid precipitate. The solid is filtered, washed with Et₂O and dried under reduced pressure giving the R isomer product as a white solid, 0.807 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 726.4 (100%) M⁺.

30

35

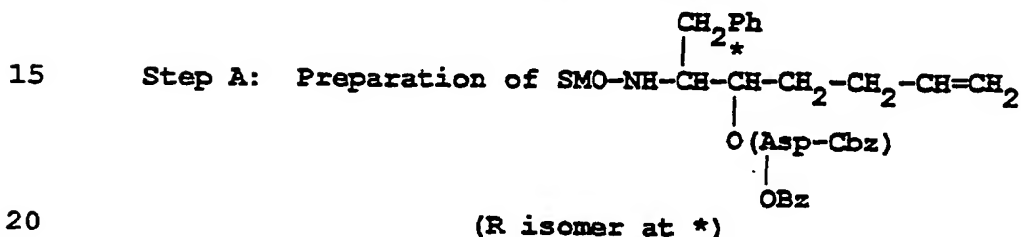
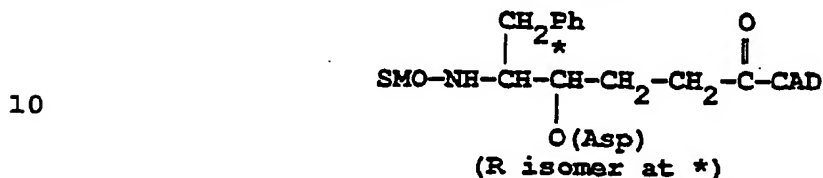


-78-

(S isomer at *) (1.05 g, 1.27 mmol) gives the S isomer product as a white solid, 0.884 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 726.3 (100%) M^+ .

5

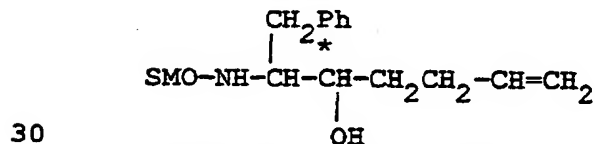
EXAMPLE 9



Cbz-Asp 2.52 g (7.05 mmol) is dissolved in

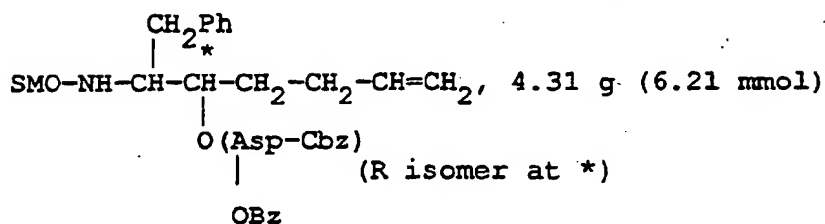
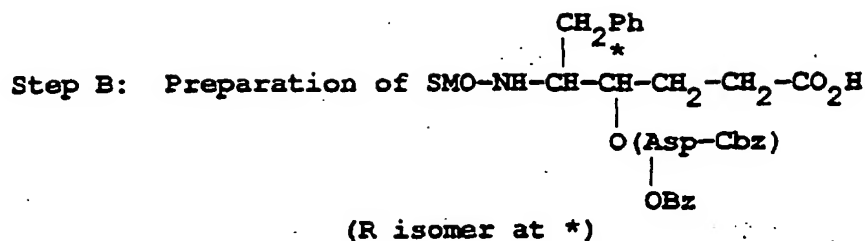
$$\begin{array}{c} \text{CH}_2\text{Ph} \\ | \\ \text{OBz} \end{array}$$

25 125 mL CH_2Cl_2 , and CDI , 1.31 g (8.11 mmol) is added and stirred for 5 minutes at room temperature.

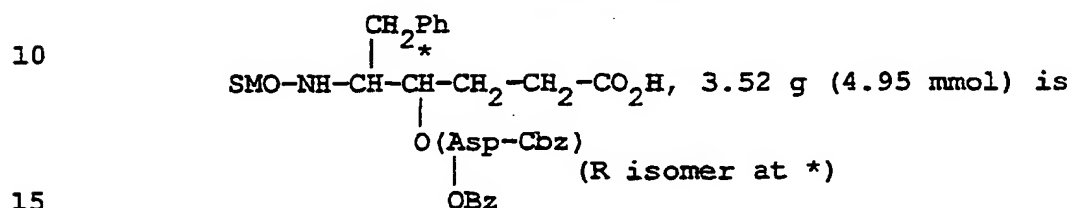
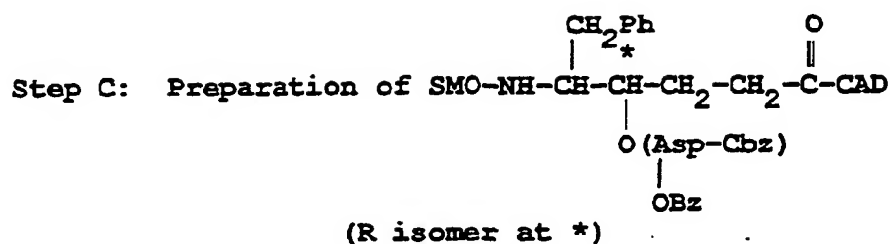


(Example I) (R Isomer at *) 2.50 g (7.05 mmol) is added, and the mixture is stirred at room temperature for 7 days. The mixture is evaporated under reduced pressure to an oil, resuspended in Et_2O , extracted with 1N citric acid, saturated NaCl solution, saturated NaHCO_3 , and saturated NaCl solution. The organic phase is dried over MgSO_4 , filtered, and evaporated to a crude gum, 4.75 g. Chromatography on silica gel, eluting with EtOAc/Hexane (20/80) gives the product as a syrup, 4.41 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 694.0 (65.2%) M^+ .

40

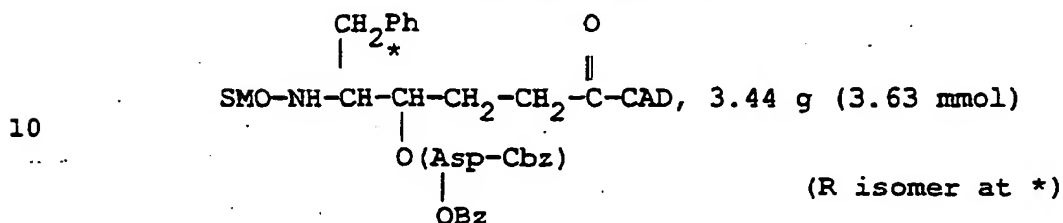
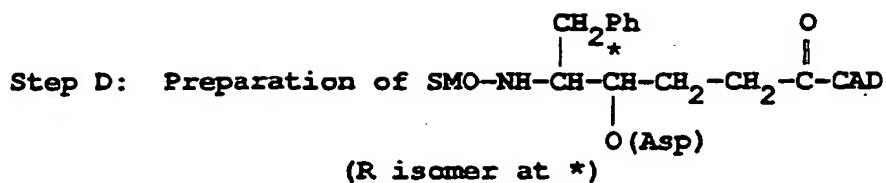


is dissolved in 170 mL acetone and cooled to 3°C. A solution of NaIO₄ 9.24 g (43.2 mmol) and RuO₂·xH₂O 0.28 g in 130 mL H₂O is added to the preceding solution, giving an exotherm which is controlled to 20°C by external cooling. After stirring at room temperature for 2 hours, the suspension is filtered through celite and evaporated under reduced pressure to remove acetone. The residue is extracted twice with Et₂O, and the extract is then washed with saturated NaCl solution, 5% sodium bisulfite solution, and saturated NaCl solution. The organic phase is dried over MgSO₄, filtered, and evaporated to a solid 3.65 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 712.0 (46.6%) M⁺.

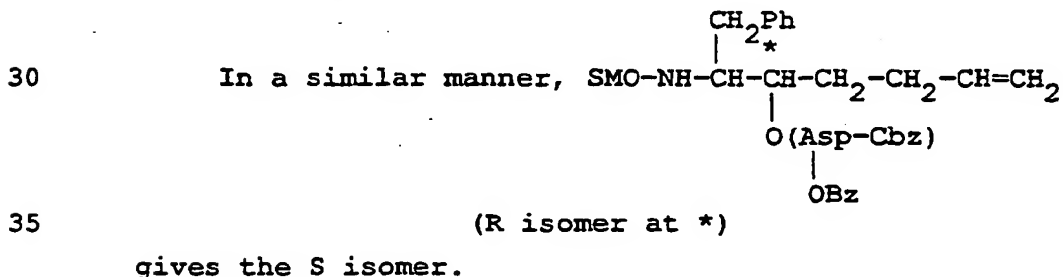


dissolved in 175 mL CH₂Cl₂, and cooled to 0°C. A solution of HOBT 0.7 g (5.19 mmol) in DMF is added, followed by DDC 1.07 g (5.19 mmol), and a solution of CAD 1.20 g (4.94 mmol) in 20 mL CH₂Cl₂/DMF. The mixture is stirred at room temperature overnight and is evaporated under reduced pressure to an oil with suspended solids. The mixture is suspended in Et₂O, filtered, and extracted with 1N citric acid, saturated NaCl solution, saturated NaHCO₃, and saturated NaCl solution. The organic phase is dried over MgSO₄, filtered, and evaporated to a white foam, 4.72 g. Chromatography on silica gel, eluting with a gradient of 25% to 50% EtOAc in Hexane gives the product as a solid, 3.43 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 937.4 (42.0%) M⁺.

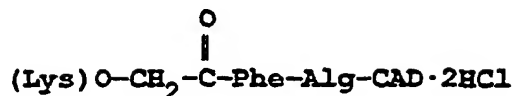
-81-



is dissolved in THF, 20% Pd on carbon catalyst is added, and the suspension is pressurized to 50 psi with H₂ gas. After 18 hours the mixture is vented, filtered, and the filtrate is evaporated under reduced pressure to a grey foam. Chromatography on silica gel, eluting with MeOH/CHCl₃ (20/80) gives the product as a grey solid. The solid is dissolved in CH₂Cl₂, filtered through charcoal, and a solid is precipitated from the filtrate by addition of Et₂O. The solid is filtered, washed with Et₂O, and dried under reduced pressure to a white solid 0.88 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 713.4 (73.5%) M⁺.



EXAMPLE 10



5

Step A: Preparation of $\text{(Lys-2Boc)O-CH}_2\text{-}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-Phe-Alg-CAD}$
 $\text{(Lys-2Boc)O-CH}_2\text{-CO}_2\text{H}$ (Example Q) (1.30 g,

10

3.2 mmol) is dissolved in 10 mL of CH_2Cl_2 and cooled to 0°C , HOBT (433 mg, 3.2 mmol), DCC (661 mg, 3.2 mmol) and DMAP (195 mg, 1.60 mmol) are added sequentially. The white suspension is stirred for 15 minutes. Phe-Alg-CAD (Example N) (780 mg,

15

1.60 mmol) in 10 mL of dry CH_2Cl_2 is added dropwise and the reaction mixture is stirred at room temperature for 3 days. The reaction is filtered

20

through Celite. The filtrate is washed with 1N HCl, saturated NaHCO_3 , and brine. The organic phase is dried with MgSO_4 and concentrated under vacuum. The crude product is purified twice by silica gel chromatography with 1% MeOH/ CH_2Cl_2 as eluent to give 610 mg of pure product; MS (FAB) 874 (M^+), 774, 674 (100%).

25

Step B: Preparation of $\text{(Lys}\cdot 2\text{HCl)O-CH}_2\text{-}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-Phe-Alg-CAD}$

30

$\text{(Lys-2Boc)O-CH}_2\text{-}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{-Phe-Alg-CAD}$ (100 mg, 0.11 mmol) is dissolved in 10 mL of dry CH_2Cl_2 and cooled to 0°C . Hydrogen chloride gas is passed through the reaction flask for 10 minutes and stirring is continued for 1 hour. A white precipitate appears and solvent is evaporated and the jelly residue is dissolved in CH_2Cl_2 and evaporated to dryness. The process is repeated several times to afford a white solid. It is washed with EtOAc/ Et_2O (1:2) and collected as fine white powder (58 mg).

40

HPLC showed 92% purity; MS (FAB) 675 (100% M⁺ free base) 675 (M⁺-H₂O).

EXAMPLE 11



10 Step A: Preparation of (Asp·Boc·t-Bu)O-CH₂- $\overset{\text{O}}{\parallel}$ -C-Phe-Alg-CAD

15 The (N-Boc- α -t-butylaspartyl) glycolate (1.01 g, 2.9 mmol) is dissolved in 10 mL of CH₂Cl₂. DCC (600 mg, 2.9 mmol), HOBT (393 mg, 2.9 mmol) and DMAP (178 mg, 1.46 mmol) are added sequentially to the reaction vessel at 0°C. After 15 minutes Phe-Alg-CAD (Example N) (850 mg, 1.74 mmol) in 10 mL of CH₂Cl₂ is added. The reaction mixture is stirred at room temperature for 2 days and worked up as usual.

20 Silica gel chromatography with 1% to 2% MeOH/CH₂Cl₂ affords 760 mg of product as a white foam; MS (FAB) 818 (M⁺ 48%), 762, 744, 718, 688, 644.

25 Step B: Preparation of (Asp·HCl)O-CH₂- $\overset{\text{O}}{\parallel}$ -C-Phe-Alg-CAD·HCl

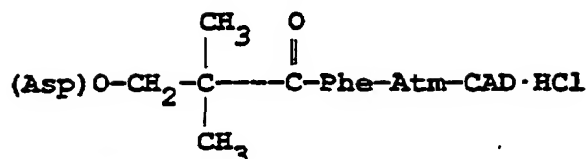
30 (Asp·Boc·t-Bu)O-CH₂- $\overset{\text{O}}{\parallel}$ -C-Phe-Alg-CAD (201 mg, 0.25 mmol) is dissolved in 20 mL of CH₂Cl₂. Hydrogen chloride gas is passed through the reaction mixture at 0°C for 15 minutes. The reaction is continuously stirred for 3 hours at room temperature. Solvent is removed and the residue is dissolved in fresh CH₂Cl₂ and evaporated. The process is repeated several

35 times to afford a white solid which is washed with Et₂O/EtOAc and collected as a fine white powder (159 mg); MS (FAB) 661 (M⁺ 91%) 643.

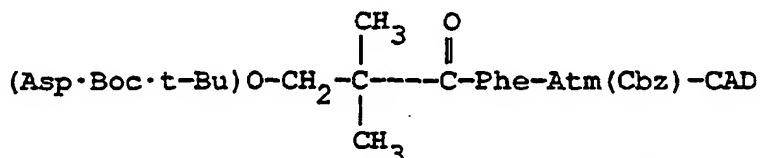
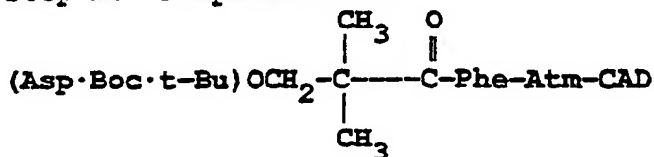
40

-84-

EXAMPLE 12

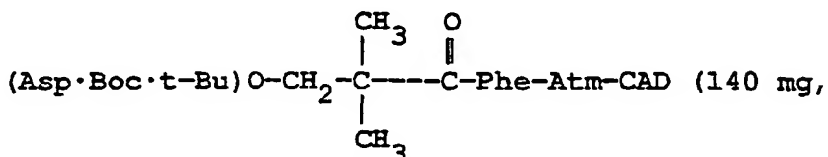
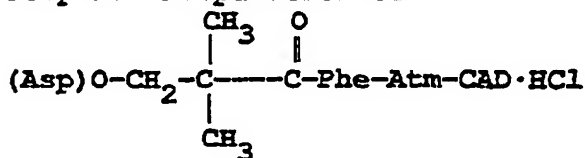


Step A: Preparation of



(373 mg, 0.35 mmol) (Example U) is dissolved in 25 mL of MeOH and 200 mg of TsOH (3 eq) and a catalytic amount of 20% palladium on carbon is added. The mixture is stirred under one atmosphere of hydrogen for 6 hours, filtered, and the solution neutralized with solid NaHCO₃. The MeOH is evaporated and the residue diluted with water and EtOAc. The mixture is extracted with EtOAc (3 x 30 mL) and dried (magnesium sulfate). The product is purified by chromatography with 3% MeOH:CH₂Cl₂ to afford 140 mg of product as a white foam; MS (FAB) 932 (M⁺).

Step B: Preparation of

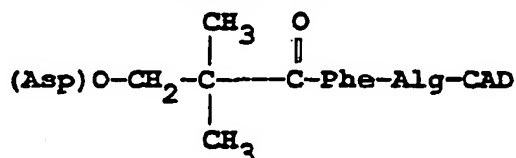


0.15 mmol) is dissolved in 10 mL of dry CH₂Cl₂, cooled to 0°C, and hydrogen chloride gas passed through for 1 hour, and the reaction stirred for 2 hours at room temperature. The solvent is

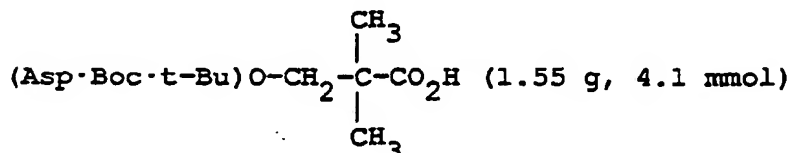
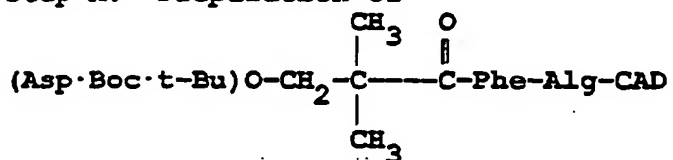
-85-

evaporated and the residue treated with CH_2Cl_2 and evaporated. The yellow solid is collected by filtration. The filter cake is washed many times with EtOAc and dried under vacuum; MS (FAB) 776 (M^{+1}), 758 (M^{+18}).

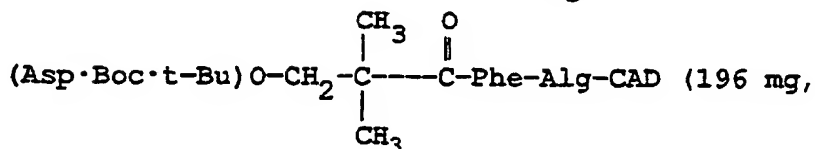
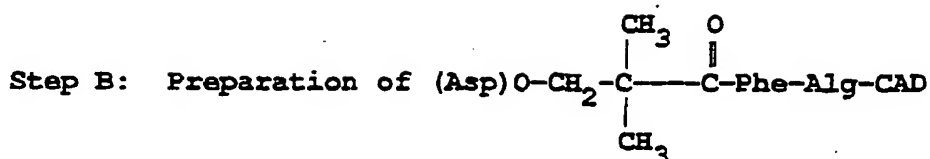
EXAMPLE 13



Step A: Preparation of



(Example S, Step B acid before coupling to Phe-O-Bz is used) is dissolved in 70 mL of CH_2Cl_2 cooled to 0°C , DCC (933 mg, 4.52 mmol), HOBT (610 mg, 4.52 mmol), DMAP (250 mg, 2.05 mmol), and Phe-Alg-CAD (1.0 g, 2.01 mmol) (Example N) are added. The mixture is stirred at room temperature for 2 days, filtered, and the solution washed with 1N HCl, saturated NaHCO_3 , NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 2% MeOH: CH_2Cl_2 to afford 1.3 g of the product as a white foam. MS (FAB) 859 (M^{+1}).



0.23 mmol) is dissolved in 15 mL of CH₂Cl₂. Hydrogen chloride gas is passed through the solution for about 30 minutes at 0°C and the mixture stirred at 0°C to room temperature for a total of 3 hours. The CH₂Cl₂ is evaporated and the residue rinsed with CH₂Cl₂ several times and the white solid collected by filtration and washed with EtOAc/Et₂O to afford 143 mg of the product as a white powder; MS (FAB) 702 (M⁺) 685 (m⁻¹⁸⁺¹).

PREPARATION OF STARTING MATERIALS

EXAMPLE A

Cbz-Ser-CAD

Cbz-Ser (500 mg, 2.09 mmol) is stirred in CH₂Cl₂ (30 mL) and DMF (10 mL) at 0°C and DCC (474 mg, 2.30 mmol, 1.1 eq), CAD (534 mg, 2.19 mmol, 1.05 eq) and HOBT (310 mg, 2.30 mmol, 1.1 eq) is added. The mixture is stirred for 2 days, filtered and evaporated. The residue is taken up in ethyl acetate (50 mL) and washed with 2 N Na₂CO₃ (75 mL), brine (75 mL), dried (MgSO₄), filtered and evaporated to afford an off-white solid. This is purified by column chromatography on silica gel eluting with 2%, 3% then 4% methanol/CH₂Cl₂ to give 600 mg of a white solid. A portion (100 mg) is recrystallized from chloroform to give 67 mg of a white solid; mp 144-146°C.

EXAMPLE B

Ser-CAD

5 Cbz-Ser-CAD (Example A) (6.8 g, 14.6 mmol) in
EtOH (100 mL) with 20% palladium on carbon (0.5 g) is
shaken under H₂ at 50 pounds per square inch (psi) at
room temperature for 1 hour. The mixture is filtered
and evaporated to leave a white foam. This is
recrystallized from ethyl acetate to give 4.03 g of a
fluffy white solid. Additional product (406 mg) is
10 obtained from the mother liquors on standing; MS
(FAB) 331.2 (100%).

EXAMPLE C

SMO-Phe-Ser-CAD

15 A mixture of SMO-Phe (European Published
Application EP 0399,556) (1.90 g, 6.06 mmol, 1.0 eq),
Ser-CAD (Example B) (6.06 mmol, 2.0 g, 1.0 eq), DCC
(1.37 g, 6.66 mmol, 1.1 eq) and HOBT (0.90 g,
6.66 mmol, 1.1 eq) is stirred in CH₂Cl₂ (100 mL) and
20 DMF (50 mL) at room temperature under N₂ for 3 days.
The solvents are evaporated and the residue taken up
in ethyl acetate (200 mL). This is washed with 2 N
Na₂CO₃ (200 mL), brine (200 mL), dried (MgSO₄),
filtered and evaporated to afford a white foam. This
25 is purified by column chromatography on silica gel
eluting with 3% then 4% MeOH/CH₂Cl₂ to give a white
foam; mp 99-102°C.

EXAMPLE D

SMO-Phe-Thr-CAD

30

Step A: Preparation of SMO-Phe-Thr

35 A mixture of SMO-Phe (European Published
Application EP 0399,556) (16.6 g, 53 mmol) and HOBT
(7.83 g, 58 mmol, 1.1 eq) in dichloromethane (400 mL)
and dimethylformamide (50 mL) is cooled to 0°C under
nitrogen. Threonine benzyl ester, hydrochloride
(13.6 g, 55 mmol, 1.05 eq), triethylamine (8.06 mL,

58 mmol, 1.1 eq) and DCC (12.03 g, 58 mmol, 1.1 eq) are added and the mixture stirred at 0°C for 1 hour. After warming to room temperature, the mixture is filtered and evaporated. The residue is partitioned between ethyl acetate and water, the organic layer separated, washed with 2N sodium bicarbonate, brine, dried (MgSO₄), filtered, and evaporated. The residue is purified by column chromatography on silica gel eluting with dichloromethane then 4% methanol/dichloromethane to afford 19 g of a solid. This is dissolved in methanol (300 mL) and 5% palladium on carbon (1.9 g) added. The mixture is stirred vigorously under hydrogen at room temperature for 5 hours. The mixture is filtered and evaporated to leave 14.8 g of a white solid; ¹H NMR (90 MHz, CDCl₃ + d⁶-DMSO) δ 7.10-7.50 (5H, m), 6.29 (1H, d, J 10.2Hz), 5.49 (3H, br. s), 3.90-4.55 (3H, m), 3.30-3.50 (4H, m), 2.75-3.10 (6H, m) and 1.15 (3H, d, J 6.6Hz).

20

Step B: Preparation of SMO-Phe-Thr-CAD

SMO-Phe-Thr (3.98 g, 9.57 mmol) is stirred at 0°C in DMF (30 mL) and dichloromethane (120 mL) and DCC (2.17 g, 10.5 mmol, 1.1 eq), HOBT (1.42 g, 10.5 mmol, 1.1 eq) and CAD (2.44 g, 10.1 mmol, 1.05 eq) added. The mixture is stirred at room temperature under nitrogen for 2 days and filtered. The filtrate is washed with 2N sodium carbonate (2 x 100 mL), brine (100 mL), dried (MgSO₄), filtered, and evaporated to leave an oily foam. This is purified by column chromatography on silica gel, eluting with 2% methanol/dichloromethane to give a white foam. This is crystallized from dichloromethane to give 2.41 g of a fluffy white solid; MS (FAB) 641.6 (51.3%) (M+H)⁺.

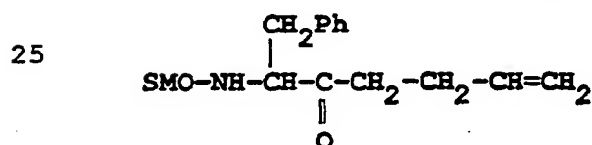
35

EXAMPLE E

SMO-Phe-N(CH₃)OCH₃

A solution of 8.0 g (25.4 mmol) of SMO-Phe
 (European Published Application EP 0399,556) in
 5 100 mL of THF/CH₂Cl₂ (1/1) is cooled to -40°C and
 4.54 g (28 mmol) of carbonyldiimidazole added. The
 mixture is then kept at -5°C for 1.5 hours. To this
 is added a solution of 2.73 g (28 mmol) of
 10 O,N-dimethylhydroxylamine, hydrochloride, and 3.23 mL
 (28 mmol) of N-methylpiperidine in 40 mL CH₂Cl₂.
 After stirring at room temperature overnight, the
 mixture is filtered and the filtrate evaporated. The
 residue is taken up in EtOAc and washed with 1 N
 citric acid, saturated NaCl, saturated NaHCO₃, and
 15 saturated NaCl. Drying over MgSO₄ and removal of the
 solvent under reduced pressure leaves 9.69 g of the
 crude product. Chromatography on silica gel, eluting
 with EtOAc/CHCl₃/MeOH (49/49/2) gives 7.56 g of the
 product as a syrup which solidifies. The structure
 20 is confirmed by NMR and mass spectroscopy; MS (FAB)
 358.1 (100%) M⁺.

EXAMPLE F

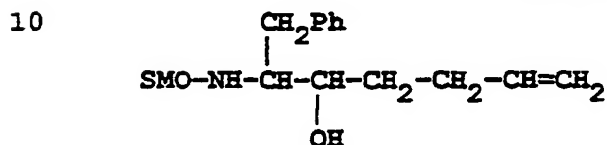


Under nitrogen, a Grignard solution prepared
 30 from 5.44 g (224 mmol) of Mg turnings and 22.7 mL
 (224 mmol) of 4-bromo-1-butene in 350 mL THF is
 heated to reflux, then cooled to -5°C and treated
 with a suspension of 20.0 g (55.9 mmol) of SMO-Phe-
 N(CH₃)OCH₃ (Example E) in 135 mL THF. After stirring
 35 at room temperature overnight, the mixture is
 evaporated to an oil. The oil is poured into a cold,
 saturated solution of NH₄Cl and extracted with EtOAc.
 The EtOAc is washed with 1 N citric acid, saturated

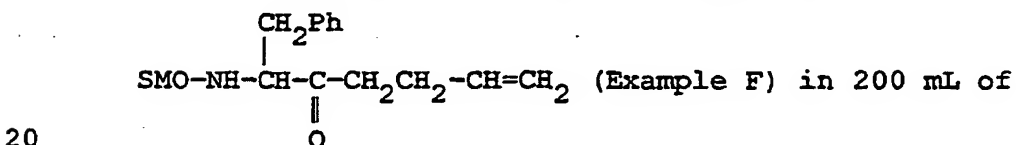
NaCl, saturated NaHCO_3 , and saturated NaCl. Drying over MgSO_4 and removal of the solvent under reduced pressure gives the crude product as an oil.

Chromatography on silica gel, eluting with
 5 hexane/EtOAc (70/30) gives 16.9 g of the product as an oil. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 353.28 M^+ .

EXAMPLE G

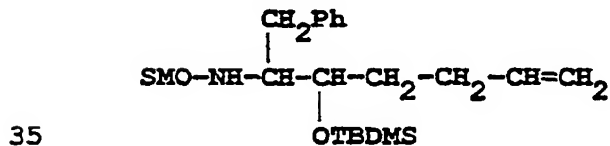


15 A solution of 6.35 g (18.0 mmol) of

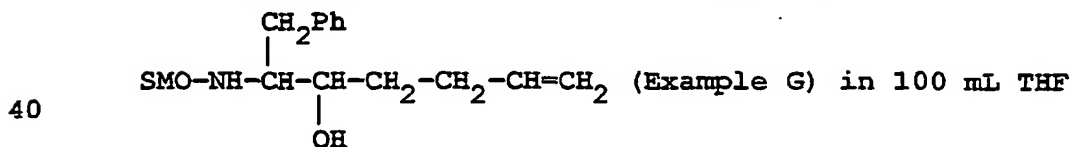


absolute EtOH is treated with 3.89 g (72.0 mmol) of KBH_4 followed by 20 mL of H_2O . After stirring at room temperature for 2.5 hours, 100 mL of acetone is added and the mixture stirred for 15 minutes. The
 25 suspension is filtered and the filtrate evaporated to an oil which solidifies. There is obtained 6.04 g of the product. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 355.25 (3.8%) M^+ .

30 EXAMPLE H



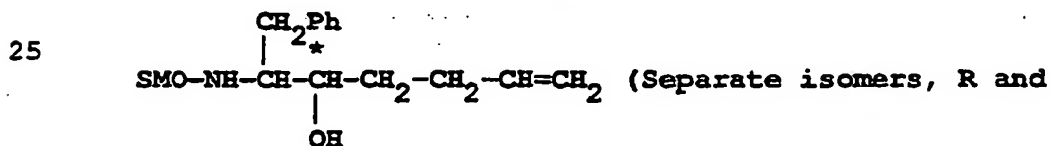
A solution of 5.95 g (16.8 mmol) of



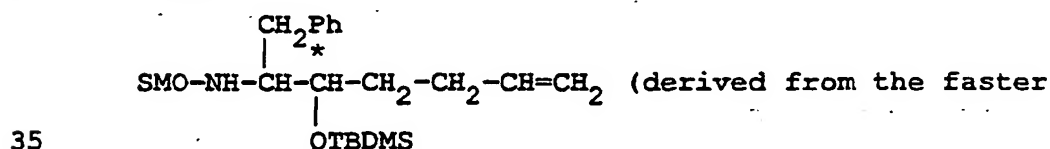
is treated with 1.48 g (22 mmol) of imidazole and 3.29 g (22 mmol) of t-butyldimethylsilyl chloride and the mixture stirred at room temperature for 2 days. An additional 0.8 g (11.8 mmol) of imidazole and 1.77 g (11.7 mmol) of t-butyldimethylsilyl chloride is then added and the mixture stirred overnight. The solvent is removed under reduced pressure and the residue suspended in EtOAc/Et₂O (1/1) and washed with H₂O, 1 N citric acid, saturated NaCl, saturated NaHCO₃, and saturated NaCl. Drying over MgSO₄ and removal of the solvent under reduced pressure gives the crude product as a mixture of diastereomers. Chromatography on silica gel, eluting with a gradient of 0% to 20% EtOAc in hexane gives 3.34 g of the faster eluting diastereomer as a glass. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 469 (100%) M⁺.

Continued elution from the column gives 2.86 g of the slower eluting diastereomer as a glass. The structure is confirmed by NMR and Mass Spectroscopy; MS (EI) 469 (100%) M⁺.

EXAMPLE I



30 S at *)

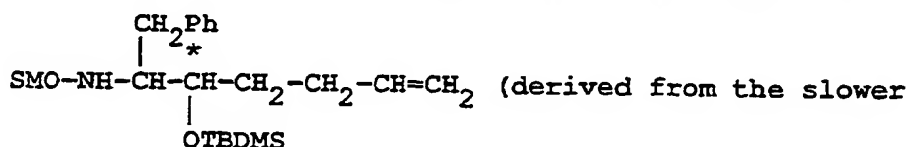


eluting R isomer at *) (Example H) 9.02 g (18.5 mmol) is dissolved in 350 mL anhydrous THF to which a solution of tetrabutylammonium fluoride (1 M in THF), 80 mL is added. After stirring at 25°C for 3 hours, the mixture is evaporated under reduced pressure to

an oil. The oil is suspended in Et₂O and extracted with 1 N citric acid, saturated NaCl solution, saturated NaHCO₃ solution and saturated NaCl solution. The organic phase is dried over anhydrous

5 MgSO₄, filtered and evaporated to a crude oil, 9 g in weight. The oil is crystallized from a mixture of Et₂O/hexane (10/90) giving a white solid, 5.55 g. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 355.3 (100%) M⁺.

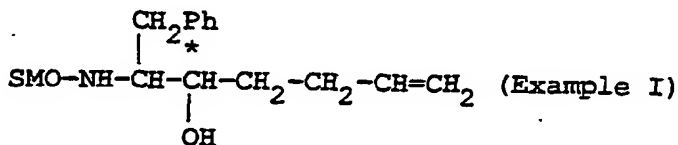
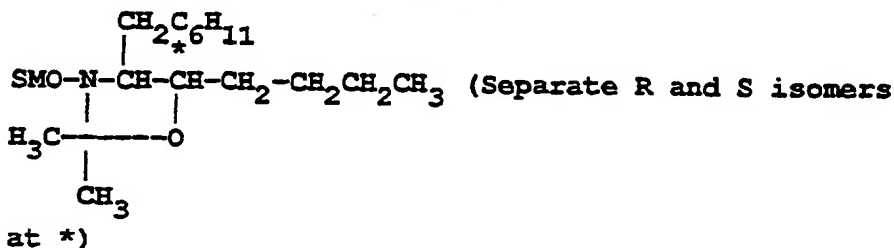
10 In an identical manner, 7.2 g (14.8 mmol) of



eluting S isomer at *) (Example H) yields 4.79 g of the corresponding S isomer product as a white solid. The structure is confirmed by NMR and Mass Spectroscopy; MS (FAB) 355.3 (100%) M⁺.

20

EXAMPLE J



35 (R isomer at *), 0.50 g (1.41 mmol) is dissolved in 40 mL of 2,2-dimethoxypropane and heated to 50°C. A trace of anhydrous p-toluenesulfonic acid is added, and the mixture is stirred for 1.25 hours. The mixture is evaporated under reduced pressure and

40 saturated NaHCO₃ solution is added to the residue. The oily suspension is extracted into Et₂O, washed with saturated NaCl solution and is evaporated to an

oil. Chromatography on silica gel, eluting with Hexane/EtOAc (5/95) gives 0.35 g of an oil. The oil is dissolved in 75 mL isopropanol and 10% Rhodium on carbon catalyst, 0.5 g is added. The mixture is placed under H₂ gas at 50 psi for 30 hours, filtered to remove the catalyst, and evaporated under reduced pressure. The residue is resuspended in 2,2-dimethoxypropane and a trace of p-toluenesulfonic acid is added. The mixture is heated to 50°C for 1 hour, and evaporated under reduced pressure. The residue is suspended in saturated NaHCO₃ solution, extracted into Et₂O, washed with saturated NaCl solution, and evaporated to an oil. Chromatography on silica gel, eluting with EtOAc/Hexane (25/75) gives the product as an oil, 0.18 g. NMR spectroscopy confirms R stereochemistry at *, and Mass Spectroscopy further confirms the structure; MS (EI) 403 (17.5%) M⁺.

In a similar manner, 0.50 g (1.41 mmoles) of

$$\begin{array}{c} \text{CH}_2\text{Ph} \\ | \\ \text{SMO-NH-CH-CH}_2\text{-CH}_2\text{-CH=CH}_2 \quad (\text{S isomer at } *) \\ | \\ \text{OH} \end{array}$$

S isomer product as an oil, 0.18 g. NMR spectroscopy confirms the structure and the S stereochemistry at *. Mass Spectroscopy further confirms the structure; MS (EI) 403 (15.4%) M⁺.

EXAMPLE K

Boc-Alg-CAD

To a solution of Boc-Alg (7.36 g, 34.23 mmol) in 200 mL of dry CH₂Cl₂ at 0°C are added DCC (8.48 g, 41.10 mmol), DMAP (2.5 g, 20.49 mmol) and HOBT (5.55 g, 41.07 mmol). The resulting white suspension is stirred for 15 minutes. CAD (8.32 g, 34.23 mmol) is dissolved in 100 mL of dry Et₂O and added to the

reaction mixture dropwise through an addition funnel. After stirring at room temperature overnight, the reaction mixture is filtered and the white solid washed with CH_2Cl_2 thoroughly. The filtrate is
5 evaporated and the residue taken up in 500 mL of EtOAc and washed with 1N HCl, saturated NaHCO_3 , and dried (MgSO_4). Solvent is removed and the residue purified by silica gel chromatography with 20% EtOAc/hexane to give 13.0 g of the product as a white
10 solid; MS (FAB) 441 (M^+), 385, 341.

EXAMPLE L

Alg-CAD

Boc-Alg-CAD (Example K) (1.01 g, 2.29 mmol) is
15 dissolved in 100 mL of dry CH_2Cl_2 . Hydrogen chloride gas is passed through this solution for 10 minutes. The reaction mixture is stirred for 3 hours. Solvent is removed and the residue dissolved in H_2O (50 mL). The aqueous solution is extracted with Et_2O
20 (50 mL x 2). The aqueous layer is then basified to pH 14 with NaOH pellets. The cloudy solution is extracted with EtOAc/ Et_2O (100 mL x 3). The organic layer is dried with MgSO_4 . Solvent is removed under reduced pressure to afford a white solid (760 mg);
25 ^1H NMR ($\text{CDCl}_3 + \text{D}_2\text{O}$) 7.5 (br d, 1H), 5.7 (m, 1H), 5.15 (m, 2H), 4.31 (m, 1H), 3.6 (m, 1H), 3.2 (br m, 2H), 2.5 (m, 2H), 1.9 (m, 1H), 1.8-1.1 (m, 14H), 0.95 (d, 3H), 0.93 (d, 3H).

30

EXAMPLE M

Boc-Phe-Alg-CAD

To a solution of Boc-Phe (5.8 g, 21.89 mmol) in 200 mL of CH_2Cl_2 at 0°C is added sequentially DMAP (1.12 g, 9.18 mmol), HOBT (3.7 g, 27.38 mmol) and DCC
35 (5.27 g, 25.54 mmol). The resulting white suspension is stirred for 15 minutes. A solution of Alg-CAD (Example L) (6.2 g, 18.23 mmol) in 100 mL of CH_2Cl_2

is added to the reaction mixture through an addition funnel. The reaction mixture is stirred vigorously at room temperature overnight. The white solid is filtered and the filtrate washed with 1 N HCl, saturated NaHCO_3 , and brine. The organic solution is dried (MgSO_4) and concentrated and further purified by silica gel chromatography to give a white solid (7.1 g); MS (FAB) 589 ($\text{M}^+ + 1$) 514.

EXAMPLE N

Phe-Alg-CAD

Boc-Phe-Alg-CAD (Example M) (7.0 g, 11.92 mmol) is dissolved in 500 mL of CH_2Cl_2 with the aid of a few drops of MeOH. Dry HCl gas is passed through solution for 15 minutes and the reaction mixture is further stirred for another 3 hours. Solvent is evaporated and the residue dissolved in H_2O (200 mL). It is then extracted with CH_2Cl_2 (3 x 250 mL). The aqueous layer is basified with NaOH pellets and extracted with CH_2Cl_2 (3 x 300 mL). The combined extracts are dried (MgSO_4) and evaporated to give 5.70 g of white solid; MS (FAB) 489 ($\text{M}^+ + 1$) 471 ($\text{M}^+ - \text{H}_2\text{O}$).

EXAMPLE O

O

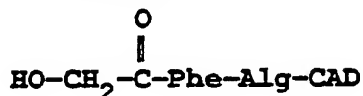
|

TBDM SOCH_2 -C-Phe-Alg-CAD

TBDM $\text{SOCH}_2\text{CO}_2\text{H}$ (1.05 g, 5.53 mmol) is dissolved in 15 mL of dry CH_2Cl_2 at 0°C . HOBT (824 mg, 6.10 mmol), DMAP (338 mg, 2.72 mmol), and DCC (11.26 g, 6.10 mmol) are added. After 15 minutes, a solution of Phe-Alg-CAD (Example N) in 15 mL of CH_2Cl_2 is added slowly. Reaction mixture is stirred at room temperature overnight. Dicyclohexylurea is filtered and the filtrate washed with 1N HCl, saturated NaHCO_3 , and dried with MgSO_4 . The solvent is removed and the residue chromatographed with 2%

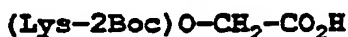
MeOH/CH₂Cl₂ to give 1.0 g of product as a white foam;
MS (FAB) 659 (M⁺) 602.

EXAMPLE P



10 TBDMSOCH₂- $\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$ -Phe-Alg-CAD (Example O) (700 mg,
1.06 mmol) is dissolved in 15 mL of MeOH. A
catalytic amount of para-toluenesulfonic acid is
added and the reaction mixture heated to 78°C for
1 hour. The methanol is evaporated and the residue
15 chromatographed over silica gel with 2% to 3%
MeOH/CH₂Cl₂ to give the product as a white foam
(325 mg). A portion of the product is recrystallized
from MeOH/EtOAc/hexane to give 16 mg of white powder;
mp 185-187°C; MS (FAB) 546 (M⁺), 528 (M⁺-H₂O).

EXAMPLE Q



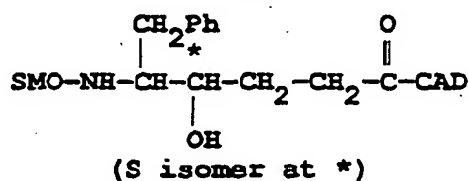
Step A: Preparation of (Lys-2Boc)O-CH₂-CO₂Bz

25 Carbonyldiimidazole (2.25 g, 13.88 mmol) is
added to the solution of Bis-Boc Lysine (4.00 g,
11.56 mmol) in 40 mL of THF at 0°C followed by a
catalytic amount of DMAP. After 10 minutes, benzyl
glycolate (1.28 g, 7.7 mmol) is added and the
solution refluxed overnight. The solvent is
30 evaporated and the residue taken up in 300 mL EtOAc.
It is washed with 1N HCl and with saturated NaHCO₃.
The organic phase is dried with MgSO₄ and
concentrated. The crude reaction product is
chromatographed with 15% EtOAc/hexane on silica gel
35 to give 3.6 g of product as a colorless oil; MS (FAB)
495 (M⁺) 439, 395.

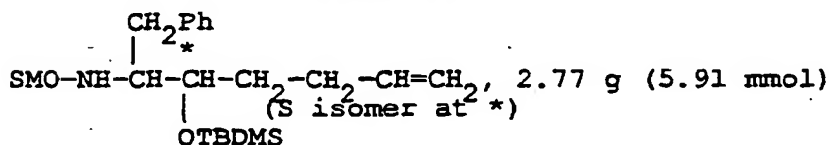
Step B: Preparation of (Lys-2Boc)O-CH₂-CO₂H

(Lys-2Boc)O-CH₂CO₂Bz (4.90 g, 9.9 mmol) is dissolved in 100 mL of EtOAc and 0.5 g of 20% palladium on carbon is added. The hydrogenolysis is carried out under 50 psi until all the starting material is consumed. The catalyst is filtered and washed thoroughly with EtOAc. Solvent is removed to leave a viscous gel (3.80 g); MS chemical ionization (CI), 408 (M⁺+1).

EXAMPLE R

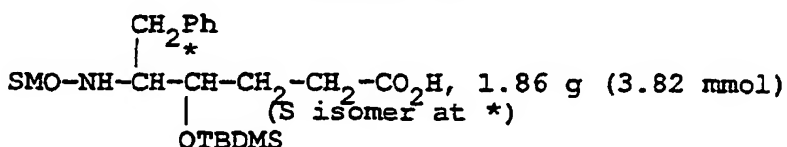
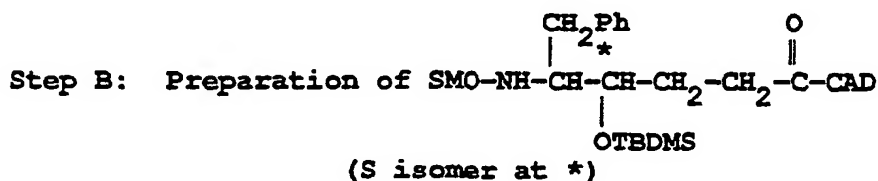


Step A: Preparation of SMO-NH-CH-CH-CH₂-CH₂-CO₂H

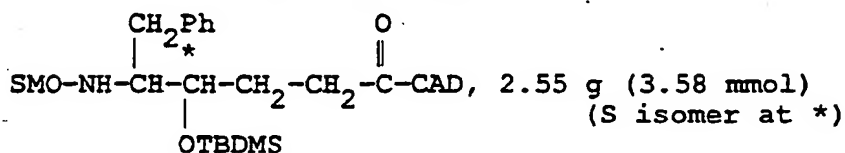
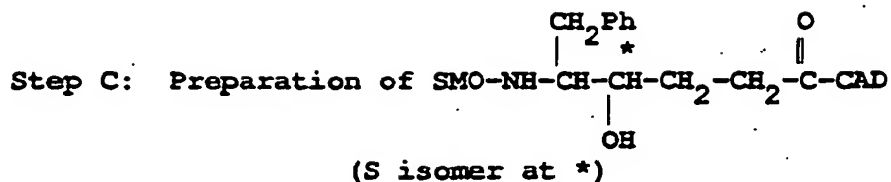
$$\begin{array}{c}
 \text{CH}_2\text{Ph} \\
 | \\
 \text{SMO-NH-CH-CH-CH}_2\text{-CH}_2\text{-CO}_2\text{H} \\
 | \\
 \text{OTBDMS} \\
 \text{(S isomer at *)}
 \end{array}$$


(Example H) is dissolved in 140 mL acetone and cooled to 15°C. NaIO₄ 9.50 g (44.41 mmol) and RuO₂·xH₂O, 0.10 g are dissolved in 60 mL H₂O and added to the previously described solution, giving an exotherm which is controlled at 20°C by external cooling over 2 hours. Isopropanol, 30 mL is added to the mixture followed by filtration through celite. The filtrate is evaporated under reduced pressure and the residue is saturated with solid NaHCO₃. The mixture is extracted exhaustively with CHCl₃ which is washed with 4% NaSO₃ solution buffered to pH 2 with concentrated HCl. The organic phase is washed with saturated NaCl solution, dried over MgSO₄, filtered, and evaporated to a solid, 2.51 g. The solid is

filtered through silica gel eluted with MeOH:CHCl₃ (10:90). Recrystallization from hexane gives a solid, 1.95 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (EI⁺) 487.25 (100.0%) M⁺.

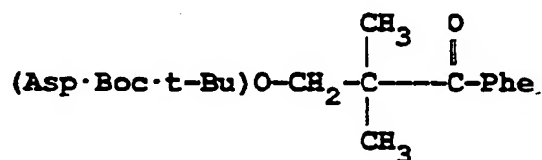


and HOBT 0.53 g (3.94 mmol) is dissolved in 5 mL DMF, diluted to 80 mL with CH₂Cl₂, and cooled to 0°C. DCC, 0.81 g (3.79 mmol) is added, followed by a solution of CAD 0.93 g (3.82 mmol) in 25 mL CH₂Cl₂/DMF. The mixture is stirred at room temperature overnight and is evaporated under reduced pressure to an oil with suspended solids. The mixture is suspended in EtOAc, filtered, and extracted with 1N citric acid, saturated NaCl solution, saturated NaHCO₃, and saturated NaCl solution. The organic phase is dried over MgSO₄, filtered, and evaporated to an oil with suspended solids. The residue is suspended in Et₂O, filtered, and evaporated under reduced pressure to a solid, 2.76 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 712.2 (100.0%) M⁺.

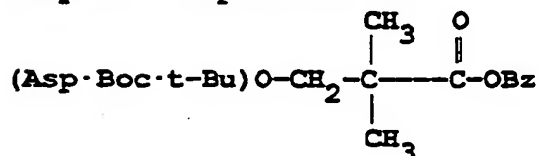


is dissolved in 70 mL 1 M t-butyl ammonium fluoride in THF. After stirring at 25°C for 6 hours, the mixture is evaporated under reduced pressure to an oil. The oil is suspended in 125 mL EtOAc and washed three times with 75 mL 1N HCl, three times with saturated NaHCO₃, and saturated NaCl. The organic phase is dried over MgSO₄, filtered, and evaporated to a solid 2.25 g. The solid is recrystallized from a mixture of CH₂Cl₂ and Et₂O, and dried under reduced pressure to a solid, 0.75 g. NMR spectroscopy confirms the structure. Mass Spectroscopy further confirms the structure; MS (FAB) 598.2 (100.0%) M⁺.

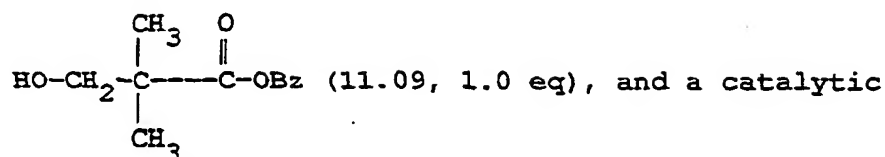
EXAMPLE S



Step A: Preparation of



N-Boc·Asp·O-t-Bu (17.1 g, 53 mmol), freed from the dicyclohexylamine salt by treatment with citric acid is dissolved in 300 mL of THF and cooled to 0°C. CDI (8.6 g), the alcohol



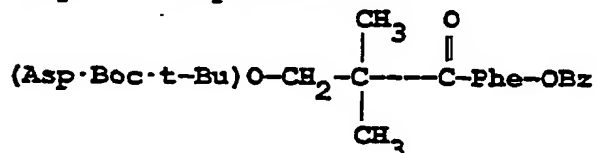
5

amount of DMAP are added and the mixture stirred at 0°C for 30 minutes and then refluxed for 24 hours. After cooling to room temperature, THF is removed by rotatory evaporation, and the residue dissolved in EtOAc and washed sequentially with 1N HCl, saturated solution of NaHCO₃, and NaCl, and dried (magnesium sulfate). The crude product is purified by chromatography with 10% to 20% EtOAc-hexane to afford 12.1 g of a white solid; MS (FAB) 367 (M⁻² t-Bu⁺¹) 324 (100%, M-Boc-t-Bu⁺¹).

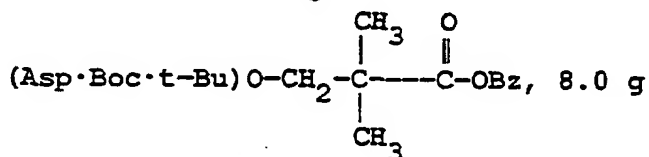
10

15

Step B: Preparation of



20



25

(16.7 mmol) is dissolved in 100 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture is stirred under one atmosphere of hydrogen for 2 hours. The mixture is filtered through celite, washed with EtOAc, and evaporated to dryness to afford an oil (~8.0 g). The crude product is dissolved in 70 mL of CH₂Cl₂, DCC (3.90 g, 1.1 eq), HOBT (2.5 g, 1.1 eq), DMAP (1.0 g, 0.5 eq), are added followed by Phe-OBz (from 5.0 g, 17.1 mmol of Phe-OBz·HCl). The mixture is stirred at room temperature overnight, DCU filtered, and the solution is washed with 1N HCl, saturated solution of NaHCO₃, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% MeOH:CH₂Cl₂ to

30

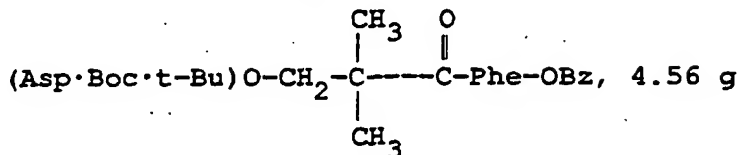
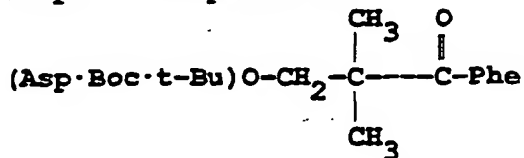
35

40

-101-

afford 11.4 g of a white solid; MS (FAB) 527
(M-Boc⁺) 471 (M-Boc-t-Bu⁺).

Step C: Preparation of



(7.27 mmol) is dissolved in 80 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture stirred under one atmosphere of hydrogen for 4 hours. The mixture is filtered through celite, the solvent evaporated, and the product used without further purification.

EXAMPLE T

Atm(Cbz)-CAD

Step A: Boc-Atm(Cbz)-CAD

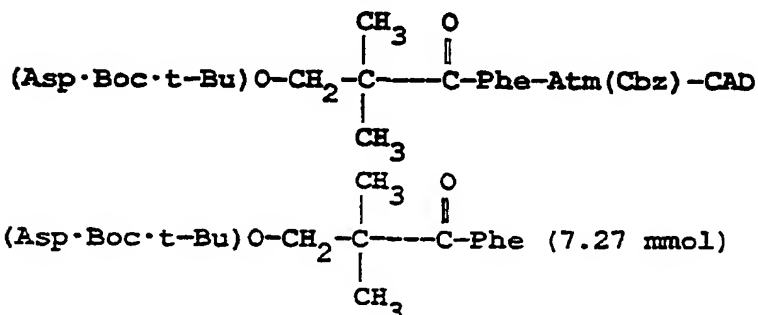
A mixture of Boc-Atm(Cbz) (European Published Patent Application EP0399,556), 6.3 g (14.9 mmol), CAD, 4.0 g (1.1 eq), DCC, 3.4 g (1.1 eq), HOBT, 2.2 g (1.1 eq), in 50 mL of DMF is stirred at room temperature overnight. The DCU is filtered and DMF removed under vacuum. The residue is taken up in 300 mL of EtOAc, washed with 1N citric acid, saturated solution of NaHCO₃, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% MeOH:CH₂Cl₂ to afford 4.22 g of product as a white foam and a second portion of 7.5 g of product; MS (FAB) 647 (M⁺).

Step B: Atm(Cbz)-CAD

Boc-Atm(Cbz)-CAD, 2.5 g (3.86 mmol) is dissolved in 40 mL of CH₂Cl₂ and 3 mL of MeOH to afford a clear

solution. Hydrogen chloride gas is passed through the solution for 10 minutes, and the reaction stirred for another 3.5 hours. The solvent is removed and the residue dissolved in 100 mL of EtOAc and 100 mL of NaHCO₃. The layers are separated and the EtOAc layer is washed with NaCl and dried (magnesium sulfate). The solvent is evaporated to afford 2.2 g of product as a pale white foam which is used without further purification.

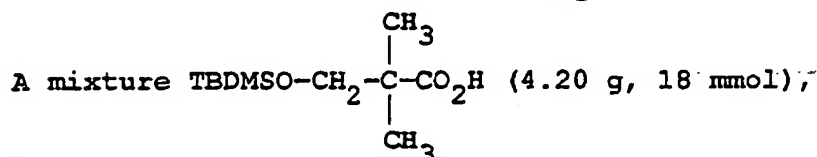
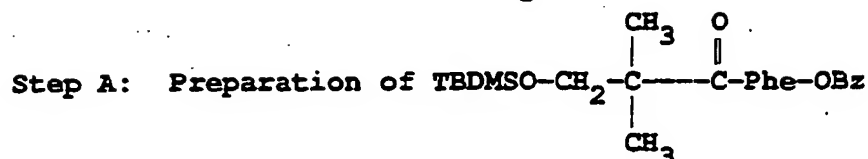
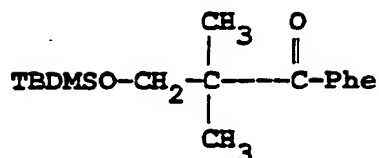
EXAMPLE U



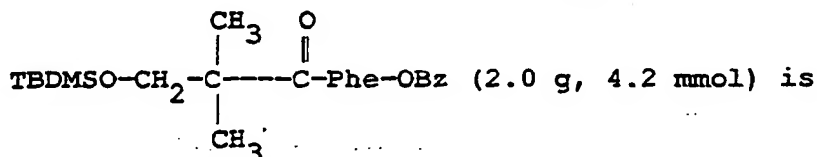
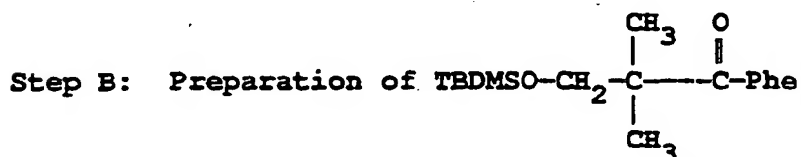
(Example S) is dissolved in 100 mL of DMF at 0°C and Atm(Cbz)-CAD (3.4 g, 6.1 mmol) (Example T), DCC (1.51 g, 7.32 mmol), and HOBT (1.0 g, 7.31 mmol) are added. The mixture is stirred at room temperature overnight. The DCU is filtered, DMF is removed by rotatory evaporation, and the residue is dissolved in 200 mL of EtOAc, washed with 1N citric acid, saturated solution of NaHCO₃ and NaCl, and dried (magnesium sulfate). The product is purified by repeated chromatography (4X) with 1% MeOH:CH₂Cl₂ to afford 4.6 g of a yellowish foam; MS (FAB) 1066 (M⁺¹).

-103-

EXAMPLE V



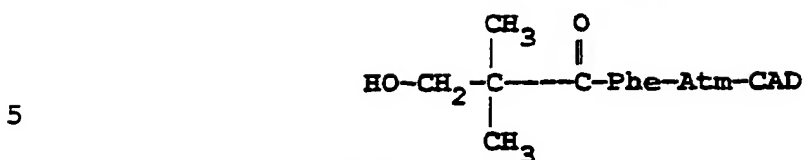
Phe-OBz (from 5.0 g, 17.1 mmol of Phe-OBz·HCl), DCC (3.9 g, 1.1 eq), HOBT (2.5 g, 1.1 eq), DMAP (1.0 g, 0.5 eq) is dissolved in 200 mL of CH_2Cl_2 . The mixture is stirred at room temperature overnight, filtered, and the solution washed with 1N HCl, saturated NaHCO_3 and NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 15% EtOAc:hexane to afford 6.94 g of the product as a clear oil; MS (FAB) 470 (M^+).



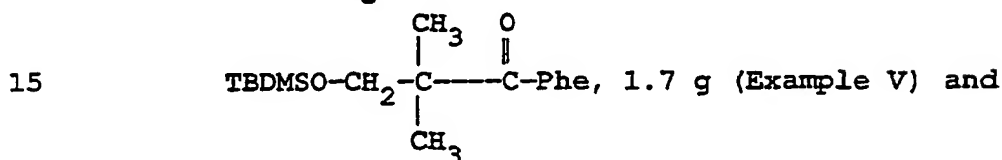
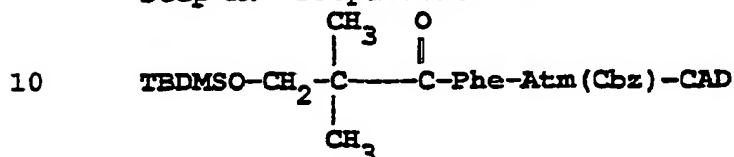
dissolved in 50 mL of EtOAc and a catalytic amount of 20% palladium on carbon is added and the mixture stirred under one atmosphere of hydrogen for 2 hours. The mixture is filtered, the solvent evaporated to afford 1.7 g of product which is used without further purification.

-104-

EXAMPLE W

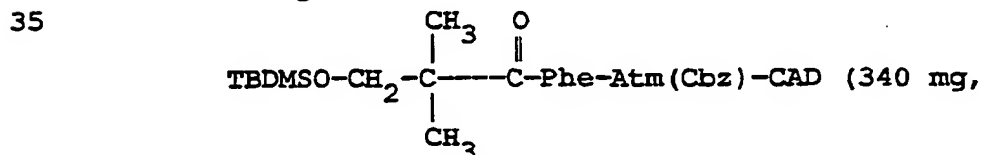
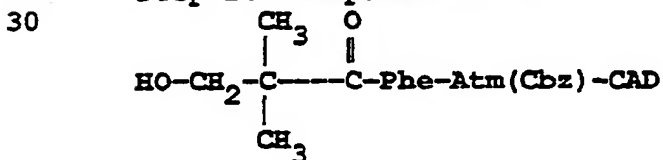


Step A: Preparation of



Atm(Cbz)-CAD (1.0 eq) (Example T) are dissolved in 50 mL of DMF, cooled to 0°C, and DCC (960 mg, 1.2 eq) and HOBT (580 mg, 1.2 eq) added. The mixture is stirred at room temperature overnight, filtered, and DMF removed by rotatory evaporation. The residue is dissolved in 100 mL of EtOAc and washed with 1N citric acid, saturated NaHCO₃ and NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% to 2% MeOH:CH₂Cl₂ to afford 1.6 g of product as a white foam; MS (FAB) 908 (M⁺).

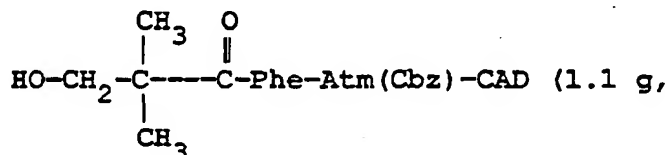
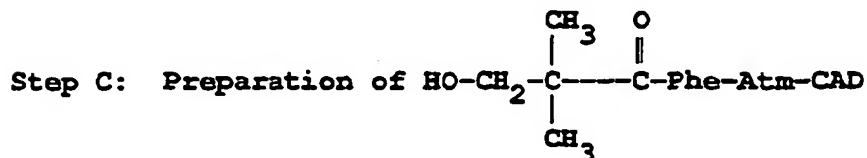
Step B: Preparation of



40 0.37 mmol) is dissolved in 15 mL of MeOH and a catalytic amount of TsOH is added. The reaction mixture is heated to 60°C for 3 hours, MeOH evaporated, and the residue taken up into water and EtOAc, and extracted with EtOAc (3 x 30 mL), and

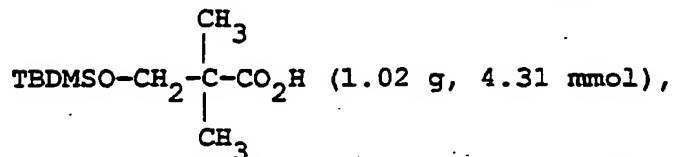
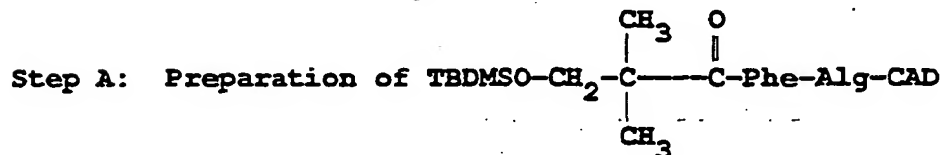
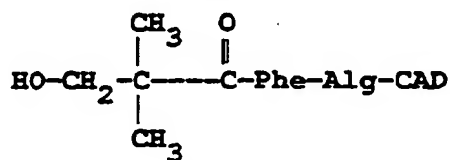
-105-

dried (magnesium sulfate). The product is purified by chromatography with 2% MeOH:CH₂Cl₂ to afford 280 mg of the product as a white foam; MS (FAB) 795 (M⁺).



1.38 mmol) is dissolved in 20 mL of dry MeOH. TsOH (530 mg, 0.2 eq) and a catalytic amount of 10% palladium on carbon are added and the mixture stirred under one atmosphere of hydrogen at room temperature for 24 hours. The mixture is filtered and the solvent evaporated. The product is purified by chromatography with 3% to 5% MeOH:CH₂Cl₂ to afford 700 mg of product as a light yellow foam; MS (CI) 660 (M⁺).

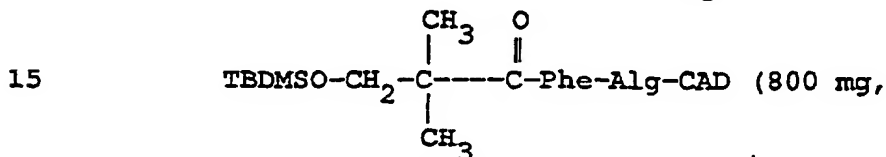
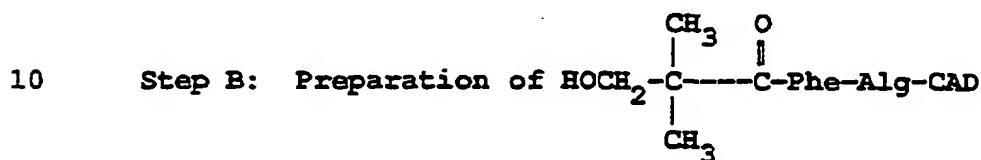
EXAMPLE X



Phe-Alg-CAD (1.00 g, 2.05 mmol) (Example N), DCC (907 mg, 4.40 mmol), HOBT (594 mg, 4.4 mmol), and DMAP (268 mg, 220 mmol) are dissolved in 20 mL of

-106-

CH₂Cl₂. The mixture is stirred at 0°C to room temperature for 40 hours, filtered, washed with 1N HCl, NaHCO₃, NaCl, and dried (magnesium sulfate). The product is purified by chromatography with 1% to 2% MeOH:CH₂Cl₂ to afford 838 mg of the product as a white foam; MS (FAB) 702 (M⁺) 684 (M⁺-18).



1.14 mmol) is dissolved in 15 mL of MeOH. A catalytic amount of TsOH is added and the mixture heated to reflux for 2 hours. The MeOH is removed by rotatory evaporation. The product is purified by chromatography with 2% to 3% MeOH:CH₂Cl₂ to afford 523 mg of the product as a white foam; MS (FAB) 588 (M⁺) 570 (M⁺-18).

25

-107-

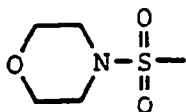
CLAIMS

1. A compound of Formula I

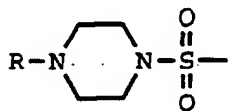
A-E-G-J

I

wherein A is

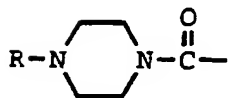
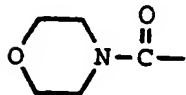
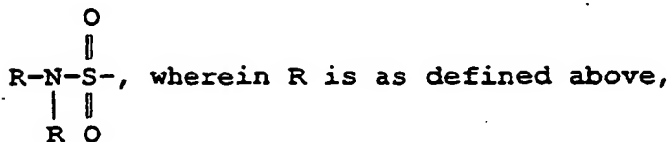


5



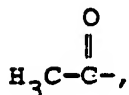
wherein R is hydrogen or
alkyl of from one to six
carbon atoms,

10

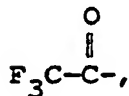


wherein R is as defined
above,

15



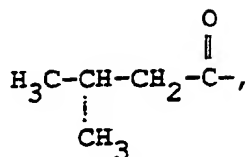
20



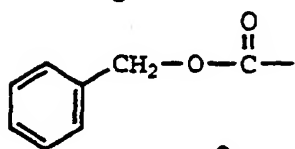
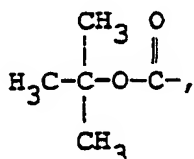
SUBSTITUTE SHEET

-108-

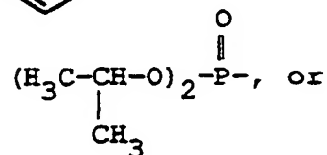
25



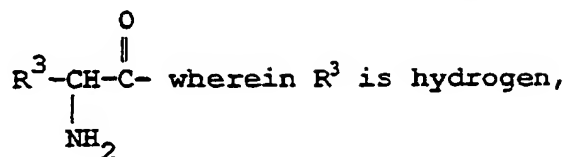
30



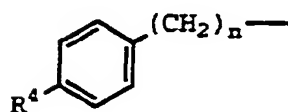
35



40

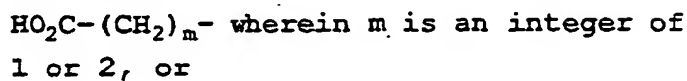
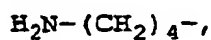


45

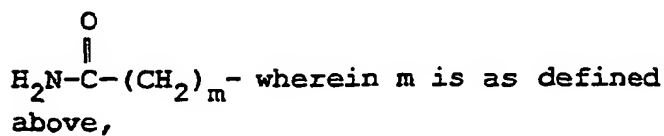


wherein n is zero or an
integer of 1 or 2 and
R⁴ is hydrogen or
hydroxyl,

50

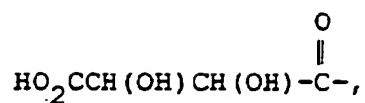


55

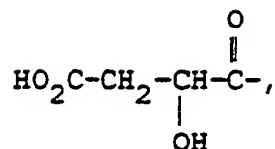


SUBSTITUTE SHEET

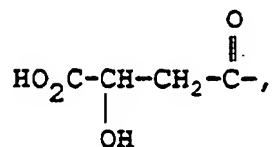
-109-



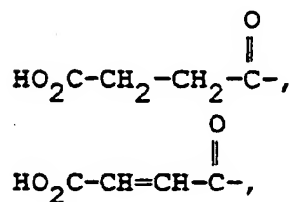
60



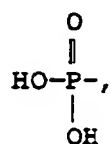
65



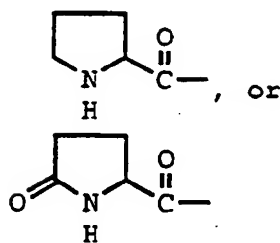
70



75



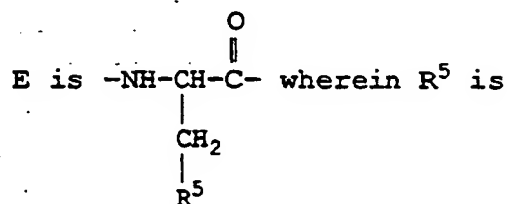
80



X is O, S, or NH, and

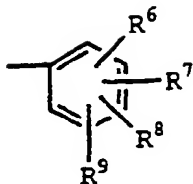
R² is alkyl of from one to six carbon atoms;

85



SUBSTITUTE SHEET

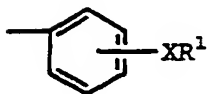
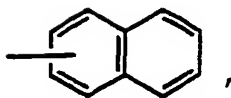
-110-



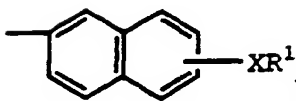
90

wherein R^6 , R^7 , R^8 , or R^9 are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

95

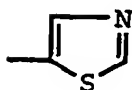
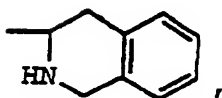


wherein R^1 and X are as defined above,



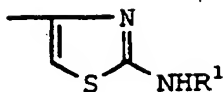
wherein R^1 and X are as defined above,

100



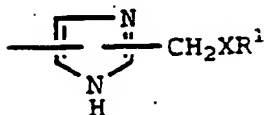
SUBSTITUTE SHEET

-111-

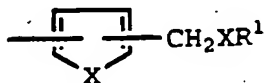


wherein R¹ is as defined above,

105

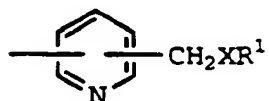


wherein X and R¹ are as defined above,



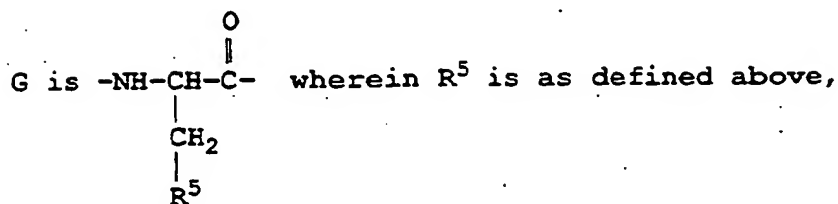
wherein R¹ and X are as defined above, or

110



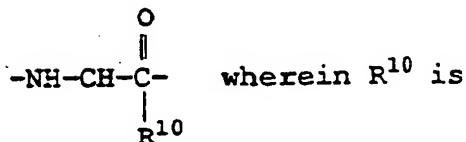
wherein R¹ and X are as defined above;

115



or

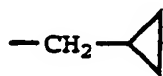
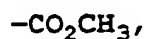
120



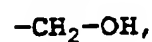
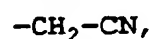
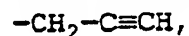
hydrogen,

125

alkyl of from one to six carbon atoms,



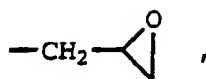
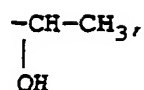
130



SUBSTITUTE SHEET

-112-

135



140

$\text{--CH}_2\text{--CH}_2\text{X--R}^1$ wherein X and R^1 are as defined above,

$\text{--CH}_2\text{X--R}^1$ wherein X and R^1 are as defined above,

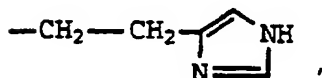
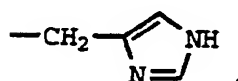
--CHX--R^1 wherein X and R^1 are as defined above,

145

$\text{--CH}_2\text{--CH}_2\text{CH}_2\text{CH}_2\text{--NH}_2$,

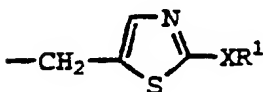
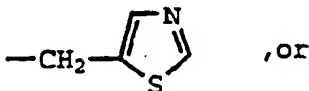
$\text{--CH}_2\text{--CH}_2\text{--S(O)}_n\text{--R}^1$ wherein n and R^1 are as defined above,

$\text{--(CH}_2)_n\text{--CONH}_2$ wherein n is as defined above,



150

wherein R^1 is as defined above,



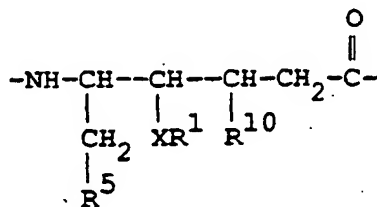
wherein X and R^1 are as defined above;

SUBSTITUTE SHEET

-113-

alternatively, E-G is

155

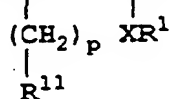


160

wherein R^1 , X, R^5 , and R^{10} are as defined above;

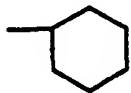
J is $\text{---NH---CH---CH---R}^{12}$ wherein R^{11} is

165

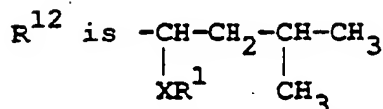
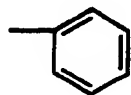


hydrogen,
alkyl,

170

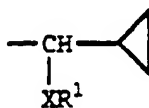


, or



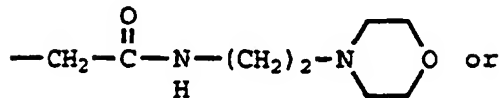
175

wherein R^1 and X are as defined above,



wherein R^1 and X are as defined above,

180

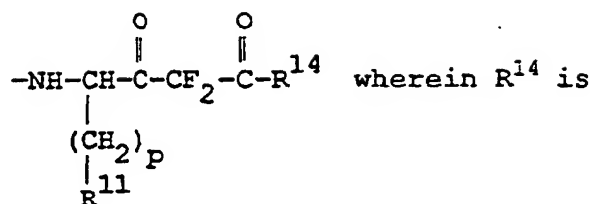


$\text{---CH}_2\text{---OC}_2\text{H}_5$ and R^1 and X are as defined above and p is zero or an integer of one, or

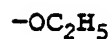
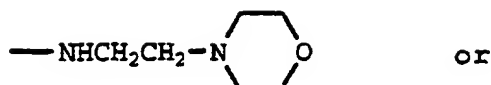
SUBSTITUTE SHEET

-114-

185



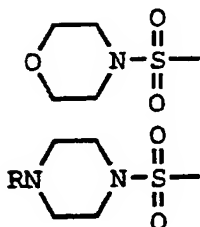
190



195

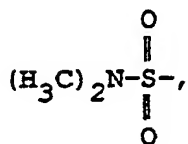
and R^{11} and p are as defined above;
provided R^1 with the exclusion of R^1 being
hydrogen is encompassed within the definition of
at least one of A, E, G, or J; or a
pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, in which A is

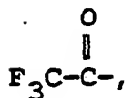
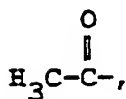


wherein R is hydrogen or alkyl of
from one to six carbon atoms,

5



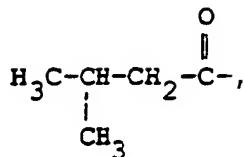
10



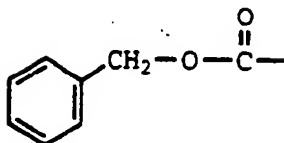
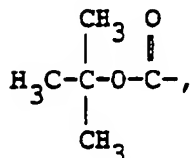
SUBSTITUTE SHEET

-115-

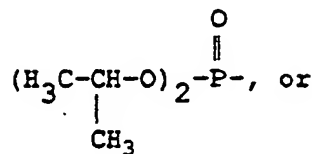
15



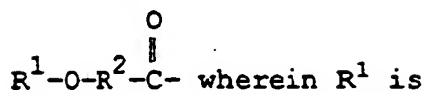
20



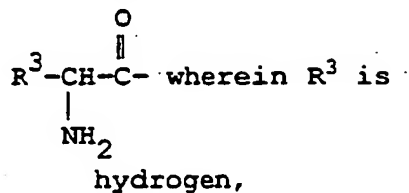
25



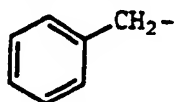
30



35



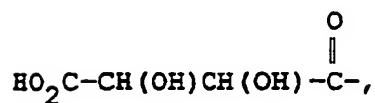
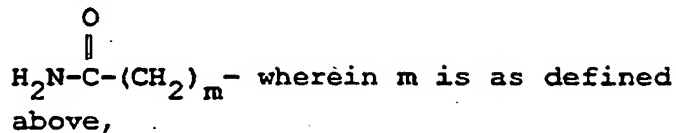
hydrogen,

CH₃-,

40

H₂N-(CH₂)₄-,HO₂C-(CH₂)_m- wherein m is an integer of
1 of 2, or

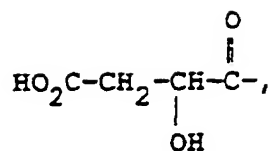
45



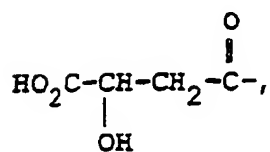
SUBSTITUTE SHEET

-116-

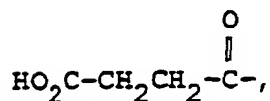
50



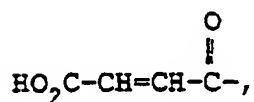
55



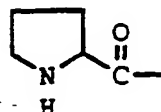
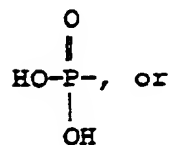
60



65



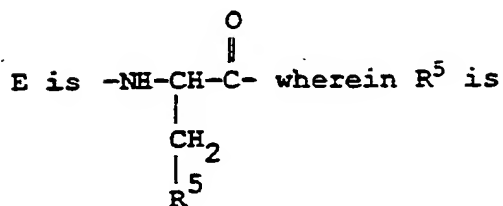
70



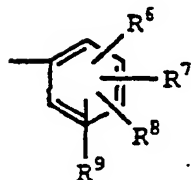
and

R^2 is alkyl of from one to six carbon atoms;

75



80



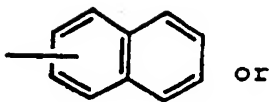
wherein R^6 , R^7 , R^8 , or R^9 are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon

85

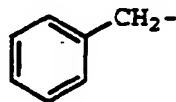
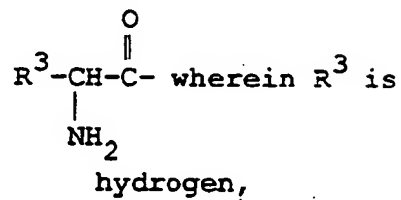
SUBSTITUTE SHEET

-117-

atoms, halogen or
trifluoromethyl,



wherein R¹ is hydrogen,

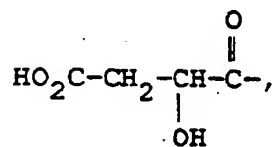
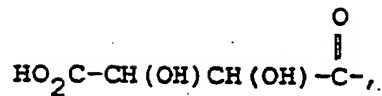
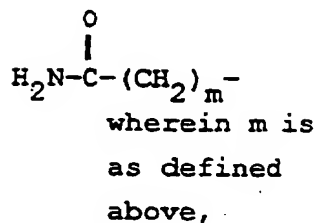


CH₃-,

H₂N-(CH₂)₄-,

HO₂C-(CH₂)ₘ-

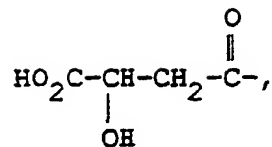
wherein m is
an integer of
1 or 2, or



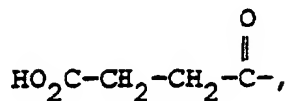
SUBSTITUTE SHEET

-118-

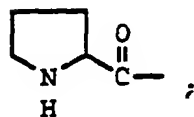
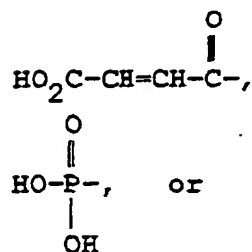
120



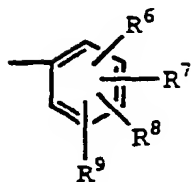
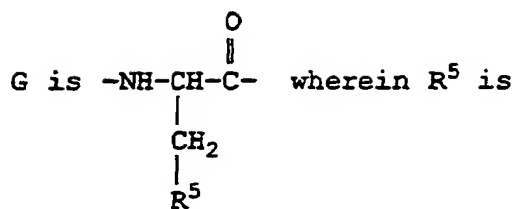
125



130



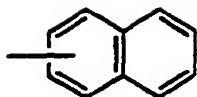
135



140

wherein R^6 , R^7 , R^8 , or R^9 are each independently hydrogen, alkyl of from one to six carbon atoms, alkoxy of from one to six carbon atoms, halogen, or trifluoromethyl,

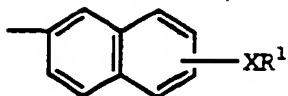
145



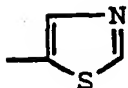
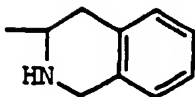
-119-



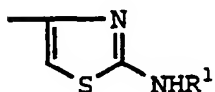
wherein X is O, S, or NH and
R¹ is as defined above



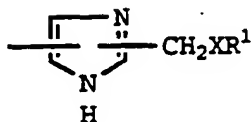
wherein R¹ and X are as
defined above,



150

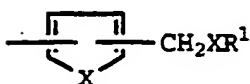


wherein R¹ is as defined
above,



wherein X and R¹ are as
defined above,

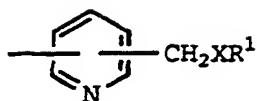
155



wherein R¹ and X are as
defined above,

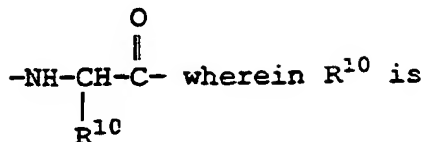
SUBSTITUTE SHEET

-120-



wherein R^1 and X are as defined above, or

160

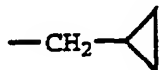


hydrogen,

alkyl of from one to six carbon atoms,

165

$-\text{CO}_2\text{CH}_3$,



170

$-\text{CH}_2-\text{CH}=\text{CH}_2$,

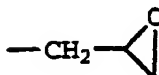
$-\text{CH}_2-\text{C}\equiv\text{CH}$,

$-\text{CH}_2-\text{CN}$,

$-\text{CH}_2-\text{OH}$,

$-\text{CH}-\text{CH}_3$,

$\begin{array}{c} | \\ \text{OH} \end{array}$



175

$-\text{CH}_2-\text{CH}_2\text{X}-R^1$ wherein X and R^1 are as defined above,

$-\text{CH}_2\text{X}-R^1$ wherein X and R^1 are as defined above,

180

$-\text{CH}-\text{X}-R^1$ wherein X and R^1 are as defined above,

$\begin{array}{c} | \\ \text{CH}_3 \end{array}$

above,

$-\text{CH}_2-\text{CH}_2\text{CH}_2\text{CH}_2-\text{NH}_2$,

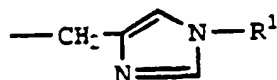
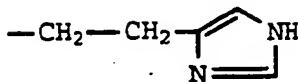
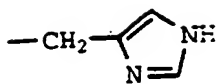
185

$-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_n-R^1$ wherein n is zero or an integer of 1 or 2 and R^1 is as defined above,

$-(\text{CH}_2)_n-\text{CONH}_2$ wherein n is as defined above,

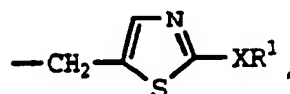
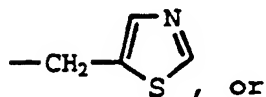
SUBSTITUTE SHEET

-121-



wherein R^1 is as defined
above,

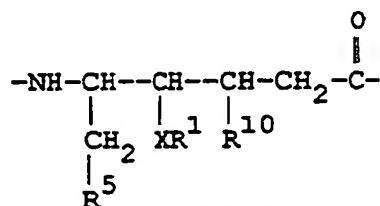
190



wherein X and R^1 are as
defined above;

alternatively, E-G is

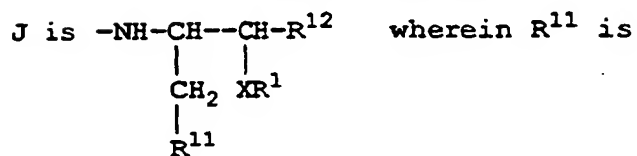
195



200

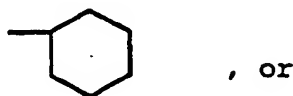
wherein R^1 , X, R^5 , and R^{10} are as
defined above;

205



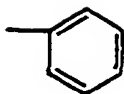
hydrogen,
alkyl,

210



SUBSTITUTE SHEET

-122-



215 R^{12} is $\begin{array}{c} -CH-CH_2-CH-CH_3 \\ | \quad | \\ OR^1 \quad CH_3 \end{array}$ wherein R^1 is as defined above,

220 $\begin{array}{c} -CH_2- \\ | \\ OR^1 \end{array}$ wherein R^1 is as defined above,
 $\begin{array}{c} -CH_2-C(=O)-N-(CH_2)_2-N \\ | \quad | \\ H \quad O \end{array}$ or
 $-CH_2-OC_2H_5$ and R^1 and X are as defined above
or

225 $\begin{array}{c} O \quad O \\ || \quad || \\ -NH-CH-C-CF_2-C-R^{14} \\ | \\ CH_2 \\ | \\ R^{11} \end{array}$ wherein R^{14} is

$-NHCH_2CH_2-N$ or

230 $-OC_2H_5$ and R^{11} is as defined above; provided
 R^1 with the exclusion of R^1 being hydrogen
is encompassed within the definition of at
least one of A, E, G, or J.

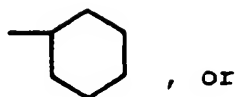
3. A compound according to Claim 2, in which J is

5 $\begin{array}{c} -NH-CH-CH-R^{12} \\ | \quad | \\ CH_2 \quad XR^1 \\ | \\ R^{11} \end{array}$ wherein R^{11} is
alkyl,

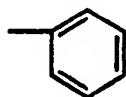
, or

SUBSTITUTE SHEET

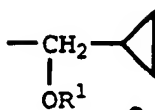
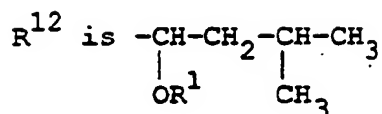
-123-



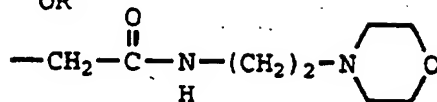
, or



10



or

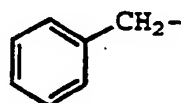
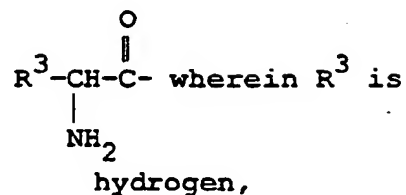


and

15

 R_1 is hydrogen,

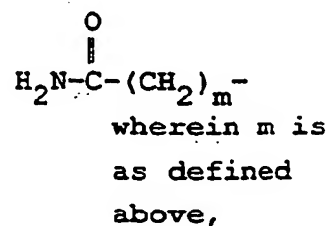
20

 $\text{CH}_3\text{---},$ $\text{H}_2\text{N---(CH}_2)_4\text{---},$ $\text{HO}_2\text{C---(CH}_2)_m\text{---}$

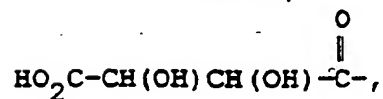
25

wherein m is
an integer of
1 or 2, or

30



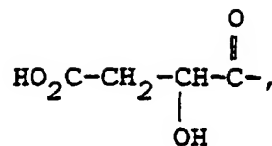
35



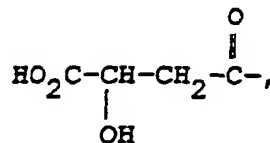
SUBSTITUTE SHEET

-124-

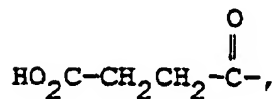
40



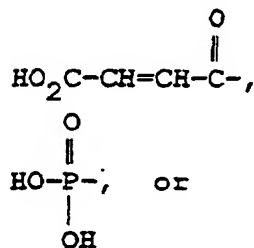
45



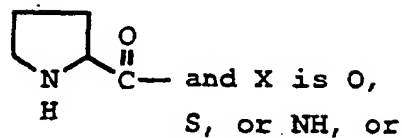
50



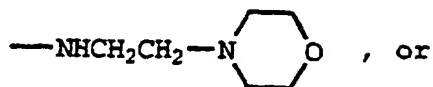
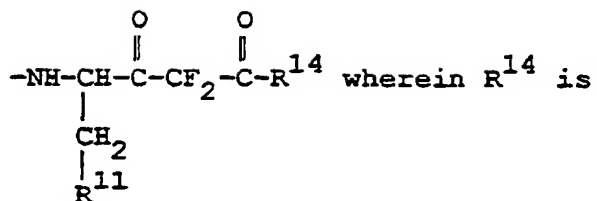
55



60



65



70

$-\text{OC}_2\text{H}_5$ and
 R^{11} is as defined above.

4. A compound according to Claim 3 selected from the group consisting of:
 SMO-Phe-Ser(Phe)-CAD;
 SMO-Phe-Ser(Gln)-CAD;

SUBSTITUTE SHEET

-125-

- 5 SMO-Phe-Ser(Pro)-CAD;
SMO-Phe-Ser(Glu)-CAD;
SMO-Phe-Ser(Lys)-CAD;
SMO-Phe-Ser(Asp)-CAD;
SMO-Phe-Ser(Gly)-CAD;
10 SMO-Phe-Ser(Ala)-CAD;
SMO-Phe-Ser(COCH₂CH₂CO₂H)-CAD;
SMO-Phe-Ser(P(O)(OH)₂)-CAD;
SMO-Phe-Ser(COCH(OH)CH(OH)CO₂H)-CAD;
SMO-Phe-Thr(Phe)-CAD;
15 SMO-Phe-Thr(Gln)-CAD;
SMO-Phe-Thr(Pro)-CAD;
SMO-Phe-Thr(Glu)-CAD;
SMO-Phe-Thr(Lys)-CAD;
SMO-Phe-Thr(Asp)-CAD;
20 SMO-Phe-Thr(Gly)-CAD;
SMO-Phe-Thr(Ala)-CAD;
SMO-Phe-Thr(COCH₂CH₂CO₂H)-CAD;
SMO-Phe-Thr(P(O)(OH)₂)-CAD;
SMO-Phe-Thr(COCH(OH)CH(OH)CO₂H)-CAD;
25 Boc-Tyr(Phe)-Pgy-CAD;
Boc-Tyr(Gln)-Pgy-CAD;
Boc-Tyr(Pro)-Pgy-CAD;
Boc-Tyr(Glu)-Pgy-CAD;
Boc-Tyr(Lys)-Pgy-CAD;
30 Boc-Tyr(Asp)-Pgy-CAD;
Boc-Tyr(Gly)-Pgy-CAD;
Boc-Tyr(Ala)-Pgy-CAD;
Boc-Tyr(COCH₂CH₂CO₂H)-Pgy-CAD;
Boc-Tyr(P(O)(OH)CH(OH)CO₂H)-Pgy-CAD;
35 Boc-Tyr(COCH(OH)CH(OH)CO₂H)-Pgy-CAD;
SMO-Phe-Hse(Phe)-CAD;
SMO-Phe-Hse(Gln)-CAD;
SMO-Phe-Hse(Pro)-CAD;
SMO-Phe-Hse(Glu)-CAD;
40 SMO-Phe-Hse(Lys)-CAD;

SUBSTITUTE SHEET

-126-

SMO-Phe-Hse (Asp) -CAD;
SMO-Phe-Hse (Gly) -CAD;
SMO-Phe-Hse (Ala) -CAD;
SMO-Phe-Hse (COCH₂CH₂CO₂H) -CAD;
45 SMO-Phe-Hse (P (O) (OH)₂) -CAD;
SMO-Phe-Hse (COCH (OH) CH (OH) CO₂H) -CAD;
SMO-Phe-Mal-CAD (2·Phe) ;
SMO-Phe-Mal-CAD (2·Gln) ;
SMO-Phe-Mal-CAD (2·Pro) ;
50 SMO-Phe-Mal-CAD (2·Glu) ;
SMO-Phe-Mal-CAD (2·Lys) ;
SMO-Phe-Mal-CAD (2·Asp) ;
SMO-Phe-Mal-CAD (2·Gly) ;
SMO-Phe-Mal-CAD (2·Ala) ;
55 SMO-Phe-Mal-CAD (2·COCH₂CH₂CO₂H) ;
SMO-Phe-Mal-CAD (2·P (O) (OH)₂) ;
SMO-Phe-Mal-CAD (2·COCH (OH) CH (OH) CO₂H) ;
SMO-Phe-Atm-CAD (2·Phe) ;
SMO-Phe-Atm-CAD (2·Gln) ;
60 SMO-Phe-Atm-CAD (2·Pro) ;
SMO-Phe-Atm-CAD (2·Glu) ;
SMO-Phe-Atm-CAD (2·Lys) ;
SMO-Phe-Atm-CAD (2·Asp) ;
SMO-Phe-Atm-CAD (2·Gly) ;
65 SMO-Phe-Atm-CAD (2·Ala) ;
SMO-Phe-Atm-CAD (2·COCH₂CH₂CO₂H) ;
SMO-Phe-Atm-CAD (2·P (O) (OH)₂) ;
SMO-Phe-Atm-CAD (2·COCH (OH) CH (OH) CO₂H) ;
SMO-Phe-Atm (Phe) -CAD;
70 SMO-Phe-Atm (Gln) -CAD;
SMO-Phe-Atm (Pro) -CAD;
SMO-Phe-Atm (Glu) -CAD;
SMO-Phe-Atm (Lys) -CAD;
SMO-Phe-Atm (Asp) -CAD;
75 SMO-Phe-Atm (Gly) -CAD;
SMO-Phe-Atm (Ala) -CAD;

SUBSTITUTE SHEET.

-127-

SMO-Phe-Atm(COCH₂CH₂CO₂H)-CAD;SMO-Phe-Atm(P(O)(OH)₂)-CAD;SMO-Phe-Atm(COCH(OH)CH(OH)CO₂H)-CAD;

80

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Phe})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

85

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Gln})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

90

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Pro})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

95

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Glu})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

100

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Lys})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

105

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Asp})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Gly})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Ala})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{HO}_2\text{CCH}_2\text{CH}_2\text{CO})\text{O}-\text{CH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

110

$$\begin{array}{c} \text{O} \\ \parallel \\ ((\text{HO})_2\text{P}(\text{O}))\text{OCH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{HO}_2\text{CCH}(\text{OH})\text{CH}(\text{OH})\text{CO})\text{OCH}_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

115

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Phe})\text{O}-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Gln})\text{O}-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

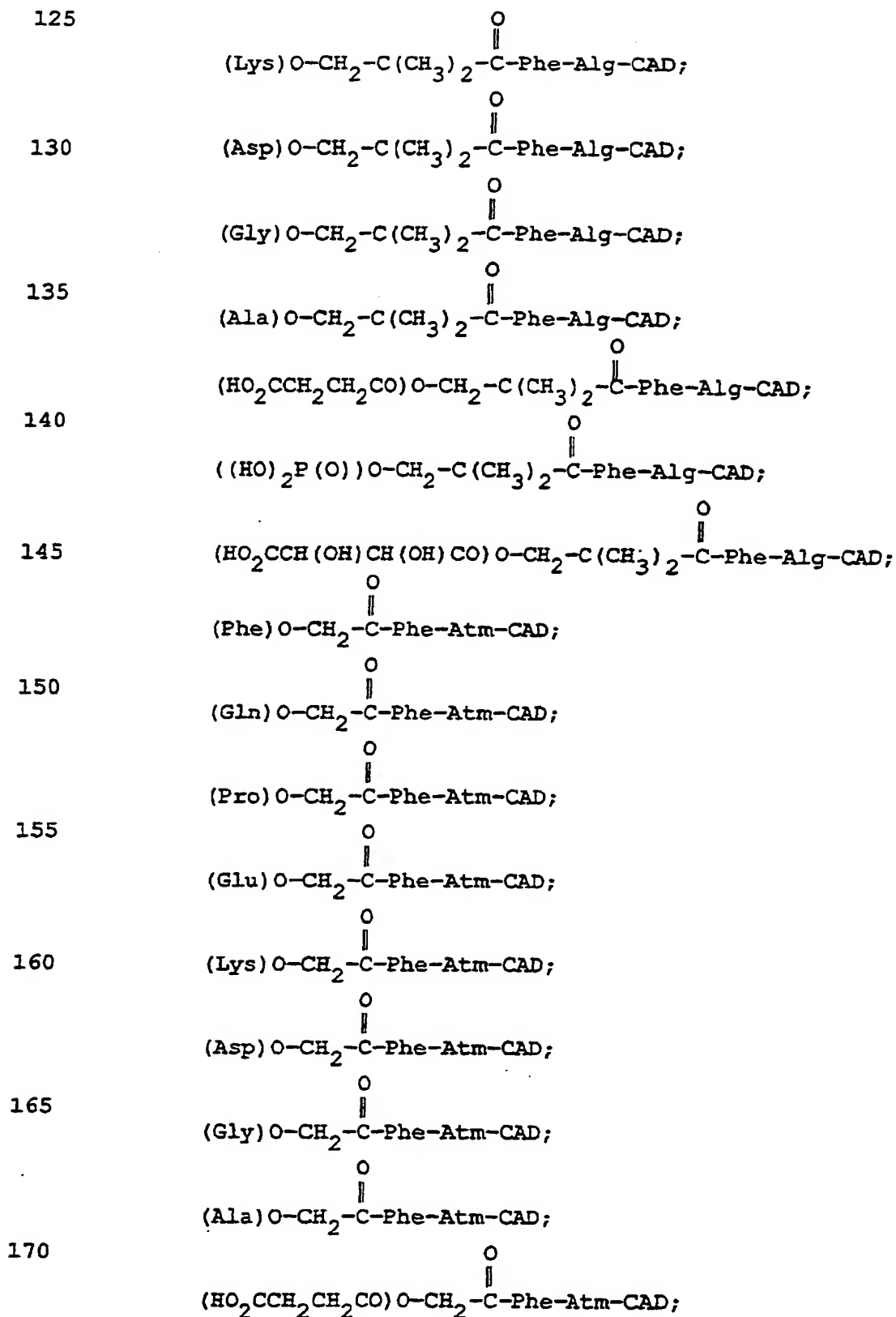
120

$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Pro})\text{O}-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

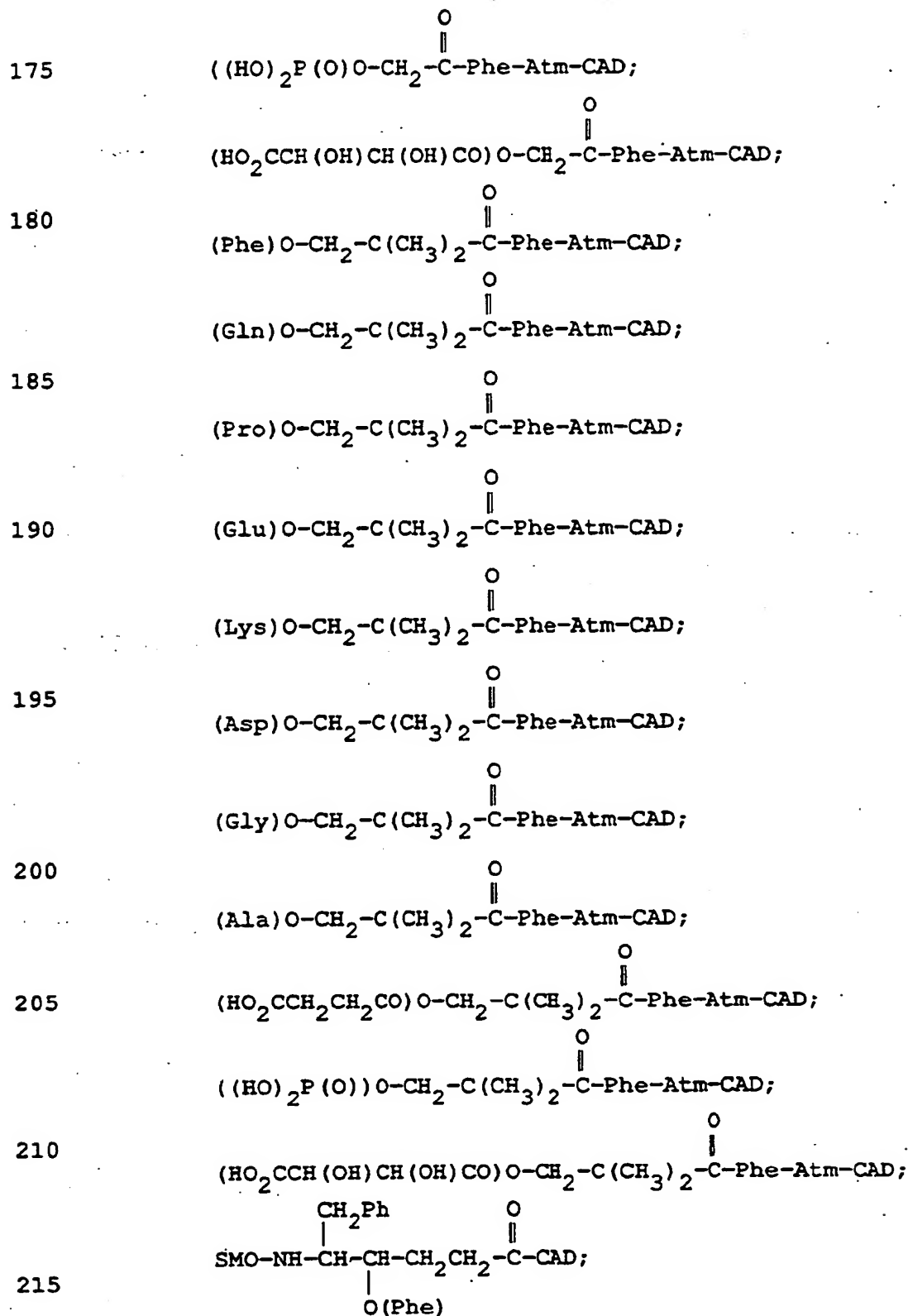
$$\begin{array}{c} \text{O} \\ \parallel \\ (\text{Glu})\text{O}-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{C}-\text{Phe}-\text{Alg}-\text{CAD}; \end{array}$$

SUBSTITUTE SHEET

-128-



-129-



SUBSTITUTE SHEET

• •

$$\text{SMO-NH-CH} \begin{array}{c} \text{CH}_2\text{Ph} \\ | \end{array} \text{CH} \begin{array}{c} | \\ \text{O(Gln)} \end{array} \text{CH}_2\text{CH}_2\text{-C(=O)-CAD;}$$
$$\text{SMO-NH-CH(CH}_2\text{Ph)-CH(O(Pro))CH}_2\text{CH}_2\text{-C(=O)-CAD;}$$
$$\text{SMO-NH}-\overset{\overset{\text{CH}_2\text{Ph}}{|}}{\underset{\underset{\text{O(Glu)}}{|}}{\text{CH}}}-\text{CH}-\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{|}}{\text{C}}-\text{CAD};$$
$$\text{SMO-NH-CH(CH}_2\text{Ph)-CH(O(Lys))-CH}_2\text{CH}_2\text{-C(=O)-CAD;}$$
$$\text{SMO-NH}-\overset{\overset{\text{CH}_2\text{Ph}}{|}}{\text{CH}}-\underset{\underset{\text{O(Asp)}}{|}}{\text{CH}}-\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{||}}{\text{C}}-\text{CAD};$$
$$\text{SMO-NH}-\overset{\overset{\text{CH}_2\text{Ph}}{|}}{\underset{\underset{\text{O(Gly)}}{|}}{\text{CH}}}-\text{CH}-\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{|}}{\text{C}}-\text{CAD};$$
$$\text{SMO-NH}-\overset{\overset{\text{CH}_2\text{Ph}}{|}}{\underset{\underset{\text{O(Ala)}}{|}}{\text{CH}}}-\text{CH}-\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{|}}{\text{C}}-\text{CAD};$$
$$\text{SMO-NH}-\overset{\overset{\text{CH}_2\text{Ph}}{|}}{\text{CH}}-\underset{\underset{\text{O}(\text{COCH}_2\text{CH}_2\text{CO}_2\text{H})}{|}}{\text{CH}}-\text{CH}_2\text{CH}_2-\overset{\overset{\text{O}}{|}}{\text{C}}-\text{CAD};$$
$$\text{SMO-NH}-\overset{\text{CH}_2\text{Ph}}{\underset{\text{O}(\text{P}(\text{O})(\text{OH})_2)}{\text{CH}}}-\text{CH}-\text{CH}_2\text{CH}_2-\overset{\text{O}}{\text{C}}-\text{CAD}; \text{ and}$$
$$\begin{array}{ccccccc} & & \text{CH}_2\text{Ph} & & & & \text{O} \\ & & | & & & & | \\ \text{SMO-NH-CH} & - & \text{CH} & - & \text{CH}_2 & \text{CH}_2 & - \text{C-CAD} \\ & & | & & & & \\ & & \text{O}(\text{COCH}(\text{OH})\text{CH}(\text{OH})\text{CO}_2\text{H}) & & & & \end{array}$$

-131-

5. A method of treating renin-associated hypertension comprising administering to a host suffering therefrom a therapeutically effect amount of a compound according to Claim 1 in unit dosage form.
6. A pharmaceutical composition adapted for administration as an antihypertensive agent comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
7. A method of treating hyperaldosteronism comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
8. A pharmaceutical composition adapted for administration as an agent for treating hyperaldosteronism comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
9. A method of treating congestive heart failure comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
10. A pharmaceutical composition adapted for administration as an agent for treating congestive heart failure comprising a therapeutically effective amount of a compound

SUBSTITUTE SHEET

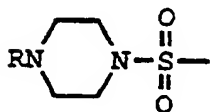
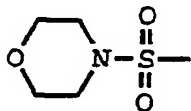
-132-

- 5 according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
11. A method of treating glaucoma comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
12. A pharmaceutical composition adapted for administration as an agent for treating glaucoma comprising a therapeutically effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.
- 5
13. A method of preparing a compound having the Formula I

A-E-G-J

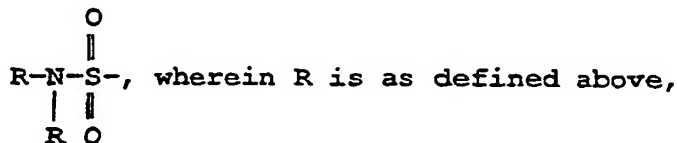
I

5 wherein A is

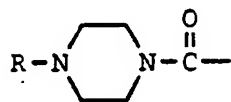
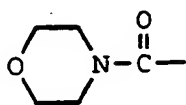


wherein R is hydrogen or alkyl of from one to six carbon atoms,

10

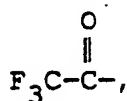
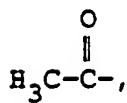


-133-

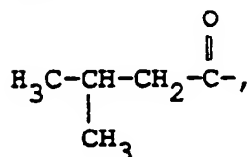


wherein R is as defined above,

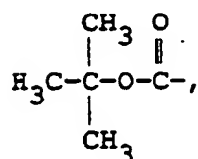
15



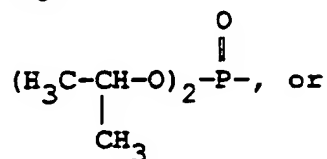
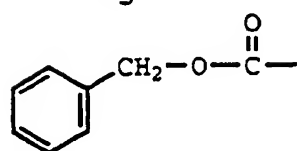
20



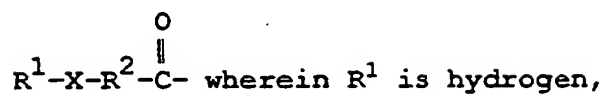
25



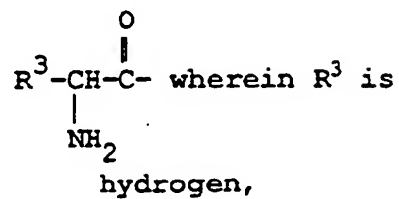
30



35



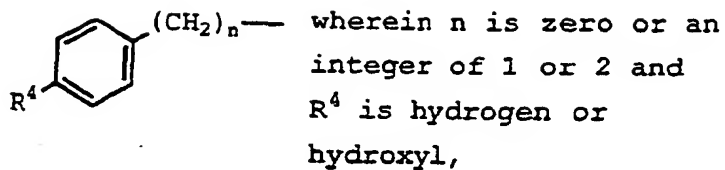
40



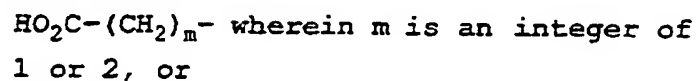
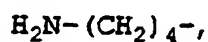
SUBSTITUTE SHEET

-134-

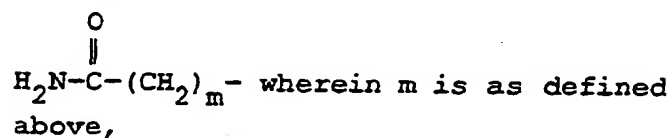
45



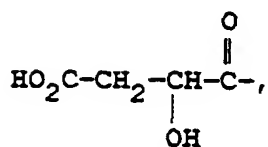
50



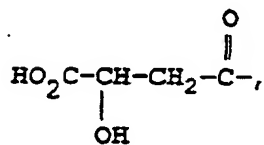
55



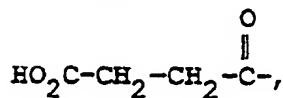
60



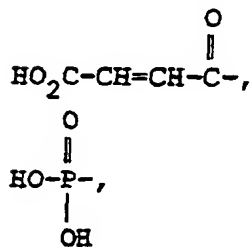
65



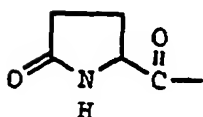
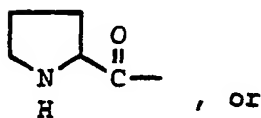
70



75



80

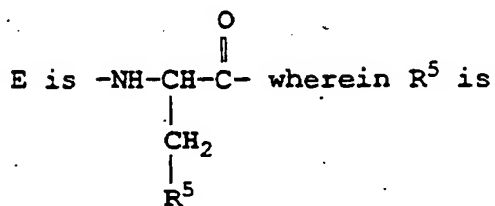


-135-

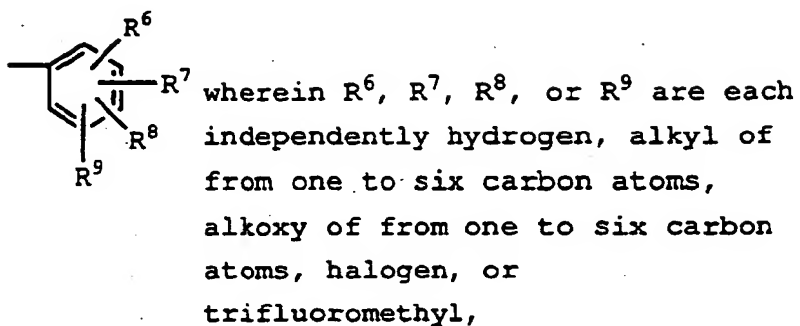
X is O, S, or NH, and

R² is alkyl of from one to six carbon atoms;

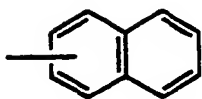
85



90

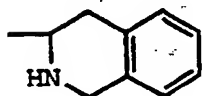
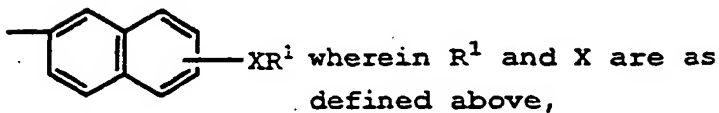


95



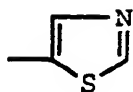
wherein R¹ and X are as defined above,

100

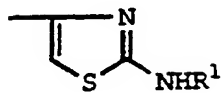


SUBSTITUTE SHEET

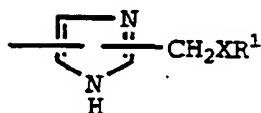
-136-



105



wherein R^1 is as defined
above,



wherein X and R^1 are as
defined above,



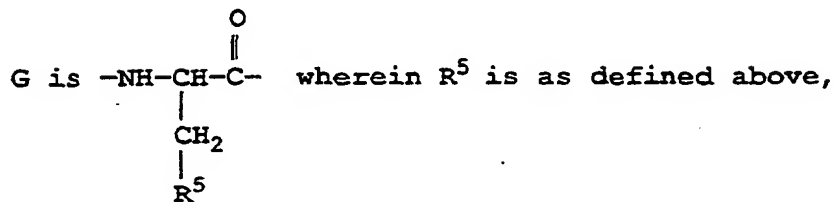
wherein R^1 and X are as
defined above, or

110



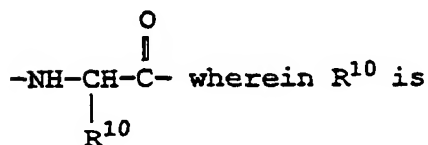
wherein R^1 and X are as
defined above;

115



or

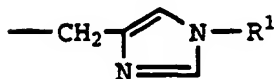
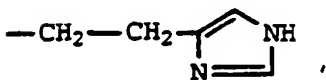
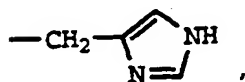
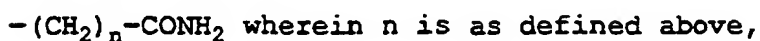
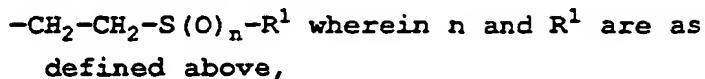
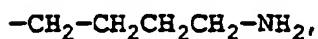
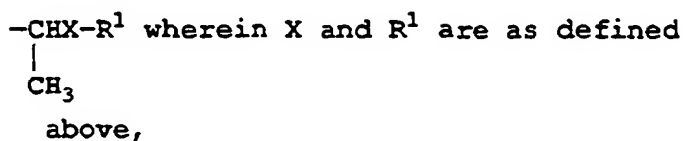
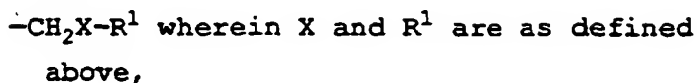
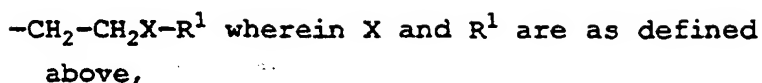
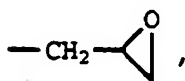
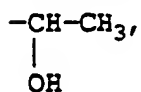
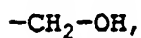
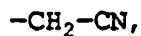
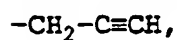
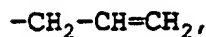
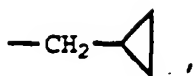
120



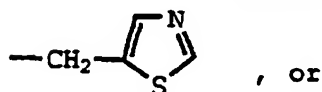
125

hydrogen,
alkyl of from one to six carbon
atoms,
 $\text{--CO}_2\text{CH}_3$,

-137-

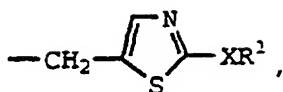


wherein R¹ is as defined above,



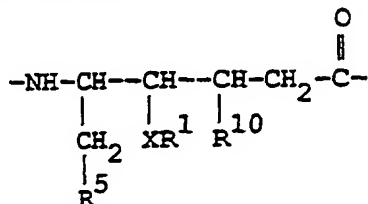
SUBSTITUTE SHEET

-138-

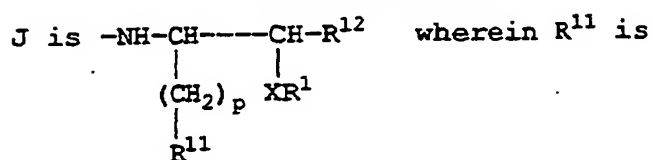


wherein X and R¹ are as defined
above;

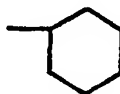
alternatively, E-G is



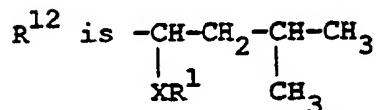
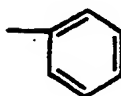
wherein R¹, X, R⁵, and R¹⁰ are as
defined above;



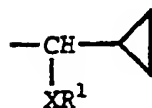
hydrogen,
alkyl,



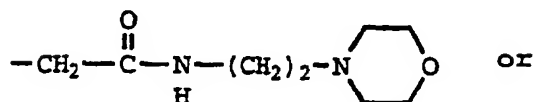
, or



wherein R¹ and X are as
defined above,



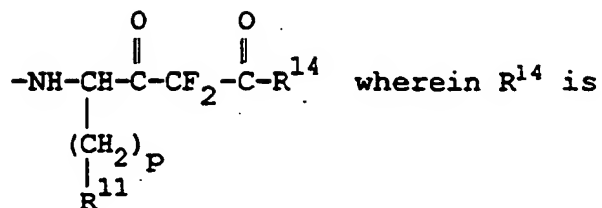
wherein R¹ and X
are as defined
above,



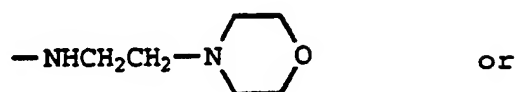
-139-

$-\text{CH}_2-\text{OC}_2\text{H}_5$ and R^1 and X are as defined above and p is zero or an integer of one, or

185



190

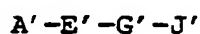


195

and R^{11} and p are as defined above; provided R^1 with the exclusion of R^1 being hydrogen is encompassed within the definition of at least one of A, E, G, or J; or a pharmaceutically acceptable salt thereof comprises:

200

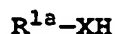
a) coupling a compound of Formula II



II

205

wherein A' , E' , G' , and J' are as defined above for A, E, G, and J provided R^1 is hydrogen and is encompassed within the definition of at least one of A' , E' , G' , or J' with a compound of Formula III



III

210

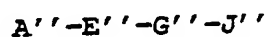
wherein R^{1a} is as defined above for R^1 but excluding R^1 is hydrogen and providing any basic

SUBSTITUTE SHEET

-140-

or acidic groups contain conventional protecting groups and X is as defined above to afford a compound of Formula IV

215



IV

220

wherein A'', E'', G'', and J'' are as defined above for A, E, G, and J provided R^{1a} is as defined above and is encompassed within the definition of at least one of A'', E'', G'' or J'';

225

b) a compound of Formula IV is deprotected in a conventional manner to afford a compound of Formula I; and if desired, converting a compound of Formula I to a corresponding pharmaceutically acceptable salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable salt to a compound of Formula I by conventional means.

230

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/07463

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: C 07 K 5/06, 11/00, C 07 C 295/26, A 61 K 37/64, 31/535, C 07 K 5/02		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	A 61 K; C 07 K	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	WO, A2, 9012804 (THE UPJOHN COMPANY) 1 November 1990, see the claims --	1-4,6,8, 10,12, 13
A	EP, A1, 0315815 (WARNER-LAMBERT COMPANY) 17 May 1989, see the whole document --	1-4,6,8, 10,12, 13
A	US, A, 5036053 (HIMMELSBACH ET AL) 30 July 1991, see the whole document --	1-4,6,8, 10,12, 13
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
17th December 1992		0 5. 01. 93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		Elisabeth Carlborg

Form PCT/ISA/210 (second sheet) (January 1985)

See notes on accompanying sheet

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		Relevant to Claim No
Category	Citation of Document, with indication, where appropriate, of the relevant passages	
A	EP, A1, 0399556 (WARNER-LAMBERT COMPANY) 28 November 1990, see the whole document	1-4,6,8, 10,12, 13

Form PCT/ISA/210 (extra sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 07463

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 5,7,9,11
because they relate to subject matter not required to be searched by this Authority, namely:
see PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 92/07463**

SA 64415

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 02/12/92
The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A2- 9012804	01/11/90	AU-D- 5407190	16/11/90
		EP-A- 0468998	05/02/92
		JP-T- 4504716	20/08/92
EP-A1- 0315815	17/05/89	AU-D- 2728188	23/05/89
		US-A- 5034512	23/07/91
		WO-A- 89/03820	05/05/89
US-A- 5036053	30/07/91	AU-B- 625456	09/07/92
		AU-D- 3463389	30/11/89
		EP-A- 0343654	29/11/89
		JP-A- 2067297	07/03/90
EP-A1- 0399556	28/11/90	AU-B- 625354	09/07/92
		AU-D- 5590890	29/11/90
		CA-A- 2017552	26/11/90
		JP-A- 3086870	11/04/91

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0470